Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700

Attorneys for Plaintiffs
Mitsubishi Tanabe Pharma Corp.,
Janssen Pharmaceuticals, Inc.,
Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International

Of Counsel:

Eric W. Dittmann
Isaac S. Ashkenazi
Dana Weir
Max H. Yusem
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166

Attorneys for Plaintiff
Mitsubishi Tanabe Pharma Corp.

Raymond N. Nimrod
Colleen Tracy James
Catherine T. Mattes
QUINN EMANUEL
URQUHART & SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010

Attorneys for Plaintiffs
Janssen Pharmaceuticals, Inc.,
Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, *et al.*, Plaintiffs, v. SANDOZ INC., *et al.*, Defendants.	**Civil Action No. 17-5319 (FLW) (DEA) (consolidated)** [redacted] **(Filed Electronically)**

PLAINTIFFS' POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF AUTHORITIES
(Continued)

Page(s)

TABLE OF AUTHORITIES
(Continued)

Page(s)

TABLE OF ABBREVIATIONS

Parties	
Janssen	Plaintiffs Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, Janssen Research and Development, LLC, and Cilag GmbH International
MTPC	Plaintiff Mitsubishi Tanabe Pharma Corp.
Plaintiffs	MTPC and Janssen
Zydus	Defendant Zydus Pharmaceuticals (U.S.A.) Inc.
Patents-in-Suit	
'788 patent	U.S. Patent No. 7,943,788, titled "Glucopyranoside Compound," which issued on May 17, 2011, from Application No. 11/045,446 (PTX-1)
'219 patent	U.S. Patent No. 8,222,219, titled "Glucopyranoside Compound," which issued on July 17, 2012, from Application No. 13/174,814 (PTX-2)
'403 patent	U.S. Patent No. 8,785,403, titled "Glucopyranoside Compound," which issued on July 22, 2014, from Application No. 13/494,602 (PTX-3)
patents-in-suit	the '788, '219, and '403 patents
asserted claims	claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent
References	
'126 patent	U.S. Patent No. 6,414,126 (PTX-36)
'117 patent	U.S. Patent No. 6,515,117 (DTX-87)
US '143	U.S. Patent Application Publication No. 2004/0138143 (PTX-64)
US '315	U.S. Patent Application Publication No. 2002/0111315 (PTX-59)
US '674	U.S. Patent Application Publication No. 2001/0041674 (PTX-58)
WO '737	International Patent Application No. WO 2003/020737 (PTX-89)
Böhm	Böhm & Klebe, *Development of New Hydrogen-Bond Descriptors and Their Application to Comparative Molecular Field Analyses*, J. Med. Chem. 45, No. 8, 1585-97 (2002) (DTX-192)

Hongu	Hongu *et al.*, *Na+-Glucose Cotransporter Inhibitors as Antidiabetic Agents. II. Synthesis and Structure-Activity Relationships of 4'-Dehydroxyphlorizin Derivatives*, Chem. Pharm. Bull. 46, No. 1, 22-33 (1998) (PTX-108)
Link	Link & Sorensen, *A method for preparing C-glycosides related to phlorizin*, Tetrahedron Letts. 41, No. 1, 9213-17 (2000) (PTX-112)
Nogrady	Nogrady & Weaver, *Medicinal Chemistry: A Molecular and Biochemical Approach* (3d 2005) (DTX-202)
Patani	Patani & LaVoie, *Bioisosterism: A Rational Approach in Drug Design*, Chem. Rev. 96, 3147-3176 (1996) (DTX-208)
Sheridan	Sheridan, *The Most Common Chemical Replacements in Drug-Like Compounds*, J. Chem. Inf. Comput. Sci. 42, No. 1, 103-08 (2002) (DTX-210)
Pleadings	
COL	Plaintiffs' Post-trial Proposed Conclusions of Law (Section VII, *infra*)
PFOF	Plaintiffs' Post-trial Proposed Findings of Fact (Sections I-VI, *infra*)
SF	Stipulation of Facts (D.I. 144, Tab 3)
Miscellaneous	
FDA	United States Food and Drug Administration
Invokana® Products	Invokana®, Invokamet®, and Invokamet® XR
POSA	person of ordinary skill in the art
Orange Book	FDA publication titled "*Approved Drug Products with Therapeutic Equivalence Evaluations*"
SGLT	sodium-glucose cotransporter
Tr.	Testimony from deposition designations
PTO	United States Patent and Trademark Office

I. The Parties and the Instant Dispute

1. The matter before the Court centers on Zydus's attempt to commercially manufacture and market generic versions of Plaintiffs' Invokana® and/or Invokamet® products before the expiration of the patents-in-suit. (*See* SF ¶ 14; D.I. 1 at 10-15.)

2. Janssen Pharmaceuticals, Inc. holds NDA No. 204042 for Invokana® (canagliflozin tablets) and NDA No. 204353 for Invokamet® (canagliflozin and metformin hydrochloride tablets). (SF ¶ 9; D.I. 1 at 7.)

3. The '788 and '219 patents are listed in the Orange Book as covering Invokana®, and the patents-in-suit are listed as covering Invokamet®. (SF ¶ 7; D.I. 1 at 7.)

4. MTPC is the lawful assignee of the patents-in-suit. (SF ¶ 6; D.I. 1 at 6.) Janssen Pharmaceuticals, Inc., Janssen Research and Development, LLC, and Cilag GmbH International are exclusive licensees of the patents-in-suit, and Janssen Pharmaceutica NV is an exclusive sublicensee of the patents-in-suit. (SF ¶ 8; D.I. 1 at 6-7.)

5. On July 20, 2017, Plaintiffs filed a patent-infringement action against Zydus arising from Zydus's filing of ANDA Nos. 210541 and 210542 with the FDA seeking approval to commercially manufacture and market generic versions of the Invokana® and Invokamet® ("Zydus's ANDA Products") before the expiration of the patents-in-suit. (SF ¶ 14; D.I. 1 at 10-15.) Zydus is the only defendant remaining in this litigation, which originally included five defendants.[1]

[1] The four other defendants previously involved in this consolidated action were Aurobindo, InvaGen, Prinston, and Sandoz. (*See* D.I. 58.) The Court entered consent judgments of infringement with permanent injunctions through patent expiration with respect to InvaGen, Prinston, and Aurobindo. (*See* D.I. 99, D.I. 102, D.I. 172.) Sandoz was dismissed pursuant to a stipulation between Plaintiffs and Sandoz after Sandoz abandoned its last-remaining defense (D.I. 129), though Sandoz continues to challenge other patents covering the Invokana® Products in Civil Action No. 17-5005, pending before Judge Bumb.

6. Zydus stipulated that its submission of ANDA Nos. 210541 and 210542 to the FDA and any commercial manufacture, use, offer for sale, sale, or importation of Zydus's ANDA Products before the expiration of the patents-in-suit would infringe the asserted claims, to the extent they are not found invalid. (*See* SF ¶ 17; D.I. 100 at 2-3.)

7. Zydus alleged at trial that the asserted claims are invalid for obviousness, and that claims 12 and 20 of the '788 patent are invalid for obviousness-type double patenting.

8. The Court held a six-day bench trial on September 24-25 and 30, October 1-2, and November 5, 2020.[2]

II. Background

A. The Patents-in-Suit and the Asserted Claims

9. The patents-in-suit have three named inventors: (1) Sumihiro Nomura;[3] (2) Eiji Kawanishi;[4] and (3) Kiichiro Ueta.[5] (*See* SF ¶¶ 23, 29, 34.)

10. Claim 12 of the '788 patent recites the chemical name for canagliflozin, "1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluoro-phenyl)-2-thienylmethyl]benzene." (SF ¶ 26; PTX-1 at 223:5-7.)

---

[2] As reflected in the Final Pretrial Order, Plaintiffs reserve their right to seek exceptional case remedies after the Court's trial decision. (D.I. 144, Tab 4 at ¶ 522 n.106, Tab 11 at ¶ 9 n.22.)

[3] Dr. Nomura (now retired from MTPC) was appointed as the group leader of a medicinal chemistry team at MTPC, whose work contributed to the discovery of canagliflozin. (Nomura Tr. 8:5-15, 17:13-20:12, 21:3-7, 22:25-23:17; *see* SF ¶¶ 23, 29, 34.)

[4] Dr. Kawanishi is a medicinal chemist who has worked in drug discovery at MTPC for almost 30 years. (Kawanishi 821:5-22, 822:8-823:5.) Dr. Kawanishi testified at trial on October 1, 2020, regarding the significant research efforts that were undertaken in connection with the SGLT project, including his conception of canagliflozin. (*See infra* Sections III.A, V.F.)

[5] Dr. Ueta was the leader of MTPC's pharmacology laboratory whose work also contributed to the discovery of canagliflozin. (Ueta Tr. 8:17-21, 11:8-21, 16:16-22; *see* SF ¶¶ 23, 29, 34.)

11. Claim 20 of the '788 patent recites a two-dimensional drawing of the chemical structure of canagliflozin. (SF ¶ 27; PTX-1 at 224:40-55.)

12. Claim 22 of the '219 patent covers a method for treating type 2 diabetes using canagliflozin. (*See* SF ¶ 32; PTX-2 at 220:45-46.)

13. Claim 26 of the '403 patent covers a pharmaceutical composition of canagliflozin in combination with metformin (a "biguanide" compound that is also used to treat type 2 diabetes). (SF ¶ 37; PTX-3 at 221:25-26.)

B. Type 2 Diabetes and Its Treatment History

14. Diabetes mellitus, more commonly referred to as "diabetes," is a complex and progressive metabolic disorder. (Gavin[6] 731:7-17; Williams 1040:25-1041:9.)

15. A person suffering from diabetes is unable to generate adequate insulin and/or use it effectively to properly regulate blood glucose levels. (Gavin 731:12-17.) As a result, blood glucose levels rise (called "hyperglycemia"), which can cause various symptoms, such as blurred vision, increased hunger, weight loss, frequent urination, and increased sugar output in the urine. (*Id*. 731:18-732:4, 741:6-9.)

16. When left unmanaged over a prolonged period of time, diabetes can cause significant long-term damage to many biological systems (including the heart, blood vessels, and kidneys), which can potentially lead to death. (*Id.* 732:5-8.)

---

[6] Dr. James Gavin is a practicing physician with nearly 50 years of experience in diabetes education and treatment research. (Gavin 728:7-9.) Some of his most notable achievements include serving as President of the American Diabetes Association from 1993-1994 and receiving both the American Diabetes Association "Lifetime Achievement in Diabetes" award and the American Association of Diabetes Educators "Living Legend in Diabetes" award. (*Id.* 727:14-728:2; PTX-25 at 2, 7.) Dr. Gavin earned a Ph.D. in Biochemistry from Emory University in 1970 and an M.D. from Duke University in 1975. (Gavin 724:25-725:6; PTX-25 at 1.)

17. There are four types of diabetes, one of which is type 2 diabetes. (*Id.* 731:10-12.) A person with type 2 diabetes may often be able to produce a reduced amount of insulin, but, over time, experiences resistance to insulin's blood sugar-lowering action and/or inadequate functioning of β cells (which are responsible for the production and release of insulin). (*Id.* 731:10-17.) Type 2 diabetes was the most common form of diabetes in the United States in the early 2000s, constituting approximately 90% of cases, which remains the case today. (*Id.* 731:10-12, 732:10-16.)

18. To diagnose diabetes and monitor the progression of the disease, doctors have used a variety of tests, including measuring blood sugar under certain conditions (such as fasting) or monitoring glycemic control through what is referred to as an "A1C" test. (*Id.* 732:17-25; Williams 1044:9-13.) A1C is a measurement of the average blood glucose (or blood sugar) level in a patient over the previous few months. (Gavin 735:12-736:3.)

19. Once diagnosed, both in the 2003 time period and today, type 2 diabetes has generally been treated in a stepwise manner. (*Id.* 736:9-19.) Typically, the initial recommendation was to incorporate diet and exercise into the patient's daily lifestyle and then, if necessary, administer a drug to help control glucose levels. (*Id.*, PDX-302; PTX-176 at 48-51.)

20. A healthcare provider would often introduce one drug at a time, usually beginning with metformin (which is still the most widely recommended initial treatment today), and then include additional agents later, if necessary. (Gavin 736:9-737:16, PDX-302; PTX-176 at 48-51.)

21. In the 2003 time period, the most commonly used type 2 diabetes drugs included biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones ("TZDs"), and meglitinides. (Gavin 736:23-737:16, PDX-302; PTX-176 at 48-51.) The FDA-approved

compounds in these classes of drugs each had certain problems and shortcomings, including administration difficulties, weight gain, hypoglycemia, gastrointestinal side effects, negative psychological impact, and/or efficacy issues. (Gavin 737:17-738:17, PDX-302-303; PTX-176 at 48-51; PTX-113 at 169; PTX-119; PTX-212; PTX-240.) As such, additional tools were required in 2003 to adequately manage type 2 diabetes and its complications. (*Id.*)

22. Invokana®, with canagliflozin as its active ingredient, was approved by the FDA on March 29, 2013. (Gavin 743:7-9, 743:20-746:2, 750:25, PDX-306; Sims 963:9-12; Williams 1055:23-25; PTX-1086 at 1; D.I. 149 at 7-9.) It was the first-ever SGLT inhibitor approved in the United States, and thus was the first in this new class to reach the market in this country. (*Id.*)

23. Invokana® acts by inhibiting SGLT2 in the kidneys (as well as having some SGLT1 inhibition activity) and suppressing glucose reabsorption. (Gavin 757:10-25; Davies 613:14-24, 614:12-615:5, Bannister Slide 98.) This leads to glucose being excreted in the urine in greater amounts, which reduces blood glucose levels. (Gavin 746:6-9; PTX-1086 at 7.)

24. Clinical data demonstrated that Invokana® significantly reduced A1C, fasting plasma glucose levels, body weight, and systolic blood pressure in diabetic patients, and that it was generally well tolerated. (Gavin 746:3-23, 765:6-12; PTX-1086 at 9-14.)

25. The Invokana® Products are currently indicated: (1) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes; (2) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease; and (3) to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2

diabetes mellitus and diabetic nephropathy with albuminuria. (Gavin 743:10-19, PDX-306; PTX-1086 at 1; PTX-1085 at 1.)

C. Overview of Medicinal Chemistry and Drug Discovery

26. Medicinal chemistry uses a multidisciplinary approach, which includes molecular biology, biochemistry, pharmacology, medicine, analytical chemistry, and organic chemistry, to identify organic compounds that treat diseases in humans. (Davies[7] 502:3-10.)

27. As Dr. Davies explained, this multidisciplinary, ***iterative, data-driven*** approach typically involves: (1) analyzing potential biological targets and known compounds in the prior art for a disease area; (2) selecting lead compounds for improvement based on known data; (3) identifying assays that can verify whether the compounds being developed have the desired effect; (4) identifying one portion of each selected lead compound to modify; (5) synthesizing, testing, and analyzing each modification to the selected lead compounds; (6) identifying a potentially promising compound for further biological development based on the testing results; (7) conducting further studies on that promising compound; and (8) advancing that compound to clinical development, if appropriate. (*Id.* 510:24-514:9, PDX-206.)

28. During the second step, only a discrete number of biological targets and corresponding compounds to investigate can be identified because of finite time and resources. (Davies 512:4-7, 650:15-24, PDX-206.)

29. After the selection of appropriate lead compounds, a series of investigations may be developed and/or conducted to examine the effect of structural modifications upon biological

[7] Dr. Stephen Davies is a chemist with more than 40 years of experience in organic and medicinal chemistry. (Davies 496:17-502:13; PTX-23.) He is currently the Waynflete Professor of Chemistry at the University of Oxford and has founded numerous successful pharmaceutical companies. (*Id.*) Dr. Davies received a B.A. in 1973 and D.Phil. in 1975, both in Chemistry, from the University of Oxford. (*Id.*)

activity, usually through a lengthy, iterative, and labor-intensive program with the goal of finding an improved candidate molecule for further evaluation. (Davies 512:4-513:18, PDX-206; *see also* Bannister 313:21-315:8 (agreeing that "drug compound discovery is a highly iterative process" where a medicinal chemist would "try [to] improve [a] starting compound").)

30. Drug discovery is a lengthy, iterative, and labor-intensive process in part because it is necessary to make modifications to one portion of the compound at a time to determine if the change was helpful, harmful, or neutral. (Davies 512:4-10, 514:14-21, PDX-206; *see also* Bannister 314:23-315:18 (agreeing that "the goal of a medicinal chemist would be to try [to] improve [a] starting compound" by changing "one area of the molecule at a time").)

31. Medicinal chemistry can be unpredictable, as demonstrated by the many examples of compounds having "similar" structures, but significantly different biological actions and activities. (Davies 508:22-510:23, PDX-204-05.) Changing any one aspect of a molecule can significantly affect the overall biological properties of a molecule by modulating its chemical, physical, and/or biological properties. (*Id.*)

32. Unpredictability and frequent failure are the unfortunate realities of medicinal chemistry as applied to new drug molecule design. (Davies 513:25-514:9, 514:22-515:2, PDX-206.) For example, one of Dr. Bannister's own references provided that, "[e]ven in the 21st century, drug design is more of a hope than an achievement." (Bannister 297:7-12; DTX-202 at 133.) Dr. Bannister also provided real-world examples of the difficulty of drug development, explaining that none of the antidiabetic projects he discussed at trial succeeded. (Bannister 104:12-105:10.)

33. As explained in more detail in Section III below, Zydus's obviousness argument ignores these many challenges in the drug-discovery process.

III. Zydus Failed to Prove Obviousness of the Asserted Claims by Clear and Convincing Evidence

34. At trial, Zydus presented a deeply flawed, hindsight-based obviousness argument, which is premised on the unfounded assumptions that: (1) a POSA seeking to develop a more favorable antidiabetic treatment option would have focused on SGLT compounds to the exclusion of all other known potential antidiabetic treatments and, in doing so, would have selected a compound lacking any known biological data (*i.e.*, the '117 patent compound) as a lead; (2) the POSA would have then made numerous, significant changes to the structure of that compound at the same time; and (3) the POSA would have reasonably expected—without any biological data—all of these significant, simultaneous changes to result in an effective SGLT inhibitor.

35. For the reasons explained below and in Sections III-V, none of the elements of Zydus's obviousness defense were supported by the evidence at trial, and Zydus failed to satisfy its heavy burden of proving obviousness by clear and convincing evidence.[8]

A. The POSA and the Problem to Be Solved with Respect to the Patents-in-Suit

36. Drs. Bannister and Davies agree that the POSA in this case would have had a graduate degree in medicinal chemistry, pharmacology, and/or a related field, with experience in the development of pharmaceutical compositions and an awareness of the antidiabetic drug field.

[8] Virtually all of the prior art references relied upon by Zydus, including the '117 patent, were considered by the PTO before the asserted claims were issued. (Bannister 273:15-276:23.) Out of sheer desperation, Zydus may attempt to support its baseless obviousness theory by referencing the PTO examiners' initial rejection of certain '788 patent claims over these references. (*See, e.g.*, Davies 703:10-21.) The examiners, however, specifically addressed the validity of genus claims covering a large number of compounds beyond canagliflozin, and never identified any specific lead compound, including the '117 patent compound. (PTX-4 at .2785, .2789.) In any event, the examiners withdrew this rejection because they did not find "sufficient guidance to arrive at the claimed compounds." (PTX-1065.0006-.0007.)

(Davies 516:9-517:4, PDX-208; Bannister 163:11-22, Bannister Slide 31.) Dr. Bannister admitted that a POSA in this case would have had a "relatively low" level of creativity. (Bannister 334:16-335:18.)

37. Although the asserted claims are entitled to a *priority date* of July 30, 2004, as Dr. Kawanishi explained, the *date of invention* occurred no later than October 29, 2003. (Kawanishi 861:16-23; Sugama[9] Tr. 56:19-59:25, 62:2-63:16, 63:24-64:9, 82:6-82:10, 82:22-83:18, 83:20-84:1, 84:7-84:14, 84:16-19, 84:22, 84:24-85:7 (confirming that Dr. Kawanishi provided him with the instructions to make canagliflozin, which he began on October 29, 2003, as reflected in Laboratory Notebook No. E0894).)[10] Although Zydus disputed this fact before trial and forced Plaintiffs to present evidence of the invention date, Zydus neither disputed this date at trial nor offered any evidence to the contrary.

38. An obviousness analysis begins with the problem faced by the POSA. (COL ¶ 216.) As Dr. Davies explained, the goal of the POSA in this case would have been "to develop a better or ***improved*** medicine for treatment of Type 2 diabetes." (Davies 516:9-517:4, 517:15-518:4, PDX-208; *see also* COL ¶ 220.) Dr. Bannister agreed that, "[w]ith whatever compound you start with," the "typical goal" of a medicinal chemist "would be to try and ***improve*** that starting compound in some regard." (Bannister 314:23-315:1; *see also id.* 322:22-25, 313:21-314:22 (testifying that the "typical approach" would be to "identify an active compound and to

[9] Dr. Hiroshi Sugama was involved in the synthesis of the compounds claimed in the patents-in-suit. (Sugama Tr. 8:20-24, 9:3-9, 14:19-15:1, 26:1-10.)

[10] The synthesis of canagliflozin began on October 29, 2003 (PTX-170 at 128), and was confirmed by November 21, 2003 (PTX-170 at 148). (Kawanishi 861:16-23.) *In vitro* efficacy data for canagliflozin was obtained a few days later, on November 26, 2003 (Ueta Tr. 210:9-18, 232:8-235:2, PTX-131 at 122-23), and *in vivo* urinary glucose excretion data obtained by November 28, 2003 (Ueta Tr. 238:15-25, 245:5-246:23, 247:5-9, PTX-132 at 40). (D.I. 150 at 4-5; D.I. 156 at 2.)

try to ***improve*** its properties").) As such, it is undisputed that, as Dr. Bannister acknowledged, "the problem to be solved that the POSA was facing was looking to positively alter the options for treating diabetes." (*Id.* 280:11-14.)

39. In direct contrast to this agreed-upon problem, Zydus alleged that a POSA would have instead been motivated to "design around" or "circumvent" the prior art while maintaining "comparable," "me too" activity. (*See, e.g.*, Bannister 175:2-176:6; Zydus's Opening 20:16-20; Zydus's Opening Slide 32.)[11] Dr. Bannister, however, agreed with Dr. Davies that designing around the legal scope of a patent would be a "real challenge" and require a "high level of creativity," which a POSA would not have possessed. (Davies 557:24-558:17; Bannister 335:19-22, 334:10-335:18 (testifying that a "POSA in this case" would have "relatively low" creativity"); COL ¶ 223.)

B. Zydus Failed to Prove That a POSA Would Have Selected the '117 Patent Compound as a Lead Compound

40. Zydus failed to prove by clear and convincing evidence that a POSA would have selected the '117 patent compound[12] as a lead compound for further development over other more favorable antidiabetic treatment options. (COL ¶¶ 221-22.) As discussed in more detail below, the evidence at trial showed that a POSA: (1) would not have focused solely on SGLT compounds; and (2) even if the POSA did exclusively focus on SGLT compounds, she would not have selected the '117 patent compound—a compound for which there was no biological data in the prior art—to the exclusion of numerous other SGLT compounds for which such data existed.

[11] Although Dr. Bannister referenced Böhm (Bannister 177:3-22; DTX-192) for his alleged motivation to "circumvent," he admitted that he did not rely on that reference "for any [specific] chemistry or scientific issue in this case" (Bannister 317:21-318:18).

[12] Zydus and Dr. Bannister referred to this compound by its "marketing name," dapagliflozin. (Bannister 277:25-278:3.) At the relevant time, however, the compound was not called dapagliflozin—instead, it was "just the structure" in the '117 patent. (*Id.* 277:22-24.)

(1) Zydus's Focus on SGLT Compounds Can Only Be in Hindsight Based on the Breadth and Diversity of Antidiabetic Research in 2003

a. Numerous Antidiabetic Research Areas Fall Within Dr. Bannister's "Just Right" Category

41. Dr. Bannister did not establish that a POSA would have focused solely on the SGLT-inhibition mechanism to the exclusion of other known and more promising options.[13] Instead, Dr. Bannister relied on a vague "Goldilocks principle," in which he claimed a POSA would have selected a lead compound based on the perception of areas that were not "too hot" or "too cold," but "just right." (Bannister 166:20-168:5, Bannister Slide 35.) Dr. Bannister did not provide any prior art support for such a "principle," which is really a thinly veiled mechanism to apply hindsight.

42. Even accepting Dr. Bannister's vague "principle," however, many categories other than SGLT inhibition would have fallen under his "just right" category (Davies 519:2-9), which Dr. Bannister did not dispute. In fact, Dr. Bannister admitted that "SGLT compounds wouldn't necessarily be the only focus of a POSA." (Bannister 280:15-25.)

43. As Dr. Davies explained, a POSA seeking to develop a more favorable antidiabetic treatment option would have considered a variety of different mechanisms of action before selecting any potential lead compound. (Davies 516:9-517:4, 548:22-549:6, 551:23-552:2, PDX-208, PDX-237.) Accordingly, Drs. Davies and Gavin provided an extensive overview of the categories of potential antidiabetic treatment options a POSA would have

[13] Zydus's counsel confirmed that Dr. Jonathan Williams was not providing a lead compound opinion from the perspective of a POSA. (Zydus's Counsel 1027:23-1028:22, 1030:14-1031:24.) Dr. Williams likewise confirmed that he had no opinion as to whether the industry was focused on SGLT compounds over other classes of compounds. (Williams 1080:5-14.)

considered, including: (1) compounds employing FDA-approved mechanisms of action that increased efficacy or reduced side effects compared to then-approved drugs; (2) compounds having mechanisms of action that, while not yet FDA-approved, were demonstrated to be viable treatment options through human clinical data reported in the prior art; or (3) compounds for which preliminary activity data at the biological target existed. (Davies 518:9-13, 518:25-519:25, 524:17-525:2, 530:5-13, PDX-209; Gavin 738:18-740:7, PDX-304.)

44. *First*, there were several distinct categories of FDA-approved therapies for treating type 2 diabetes as of 2003, including α-glucosidase inhibitors, TZDs, and meglitinides. (Davies 519:18-524:8, PDX-210-213 (identifying specific examples of compounds in this category); Gavin 739:7-19, PDX-304; *see also* PTX-100; PTX-111; PTX-240; PTX-109.) Based on what was known about their FDA-approved mechanisms of action, Drs. Davies and Gavin explained that scientists were working at the relevant time on developing new drug molecules from these classes having improved properties compared to approved drugs, as reported in the prior art. (*Id.*) Even Dr. Bannister admitted that "a POSA faced with a problem of trying to make an improved antidiabetic medication could also pursue an improvement against an existing therapy." (Bannister 283:5-13; *see also* 283:14-18 (admitting that, in his own work, he had the "goal of finding compounds that had the beneficial properties of FDA-approved drugs[,] but lack their side effects").)

45. *Second*, Dr. Bannister also agreed with Drs. Davies and Gavin that "a POSA could have also focused on" developing compounds having other, non-approved mechanisms of action during the 2003 time period, including dual PPAR agonists, GLP-1 receptor agonists, and DPP-4 inhibitors. (Bannister 283:1-4; *see also id.* 281:18-21, 282:16-18, 283:5-8; Davies 524:17-530:3, PDX-214-217 (identifying specific examples of compounds in this category); *see*

also Gavin 739:20-740:2, PDX-304; PTX-103; PTX-113; PTX-119.) Notably, when Dr. Bannister was able to provide input for his own research focused on more favorable antidiabetic treatments in the 2005-2006 time period, he "was interested in GLP-1" and worked in that area. (Bannister 281:4-11, 102:5-6, 104:17-19.)

46. *Third*, Drs. Davies and Gavin also discussed other type 2 diabetes treatment targets and mechanisms of action that the pharmaceutical industry was actively pursuing at the relevant time, including protein-tyrosine phosphatases inhibitors, retinoid X receptor modulators, glycogen phosphorylase inhibitors, glucokinase activators, and glucocorticoid receptor antagonists. (Davies 530:4-25, PDX-219-220 (identifying specific exemplary compounds in this category); Gavin 740:3-7, PDX-304; *see also* PTX-113; PTX-119; PTX-120; PTX-106.) Dr. Bannister acknowledged that these mechanisms were of interest in the prior art, and did not disagree with Dr. Davies' opinion that a POSA conducting in type 2 diabetes drug research would have considered pursuing these types of compounds. (Bannister 284:9-285:19, PDX-102.)

47. Dr. Davies identified a variety of potential lead compounds that would appear as "boulders" on Zydus's hypothetical "beach" (*e.g.*, "CKD-711a," "MCC-555," and "KAD-1229"), as well as "smaller-sized rocks" (*e.g.*, "AZ-242," "BMS 298585," "NN-2211," and "AC-2993"). (Davies 540:3-541:10, PDX-230.) Dr. Davies identified additional "small rocks," such as "T-1095," all of which would have been of greater interest to a POSA than the '117 patent's "pebble" that is the focus of Zydus's hindsight-based approach. (*Id*.)

b. Researchers Were Skeptical of SGLT Inhibitors Due to Their Counterintuitive Mechanism of Action and Lack of Human Efficacy Data

48. Although some information existed in 2003 regarding the inhibition of SGLT as a ***potential*** treatment option for type 2 diabetes,[14] unlike the first two categories of potential lead compounds described above, there was no clinical data demonstrating that this mechanism worked to treat human patients.[15] (Davies 531:19-25; *see also* Kawanishi 825:20-24.) Moreover, Dr. Gavin explained that the mechanism of SGLT inhibition was met with skepticism by researchers and clinicians working in the diabetes field during the relevant time period. (*See infra* Section V.B.)

49. As Dr. Davies explained, his analysis of review articles from 2000-2003 looking at potential type 2 diabetes targets revealed that they did not discuss SGLT inhibitors among the numerous promising examples being explored at the time. (Davies 532:1-21, 534:4-12, PDX-223.) Even Dr. Bannister admitted that he did not recall whether he was even aware of SGLT inhibitors during the relevant period (Bannister 286:11-15), despite his work on other antidiabetic targets in the late-1990s and mid-2000s (Bannister 104:9-105:10).

50. In sum, uncertainty clouded the development of SGLT inhibitors in the 2003 time period, which caused many researchers to focus on the alternative developmental candidates described above. (*See, e.g.*, Gavin 739:4-740:13, PDX-304.)

---

[14] For example, MTPC scientists had disclosed that T-1095 exhibited antidiabetic effects only in mice and rats. (*See, e.g.*, PTX-97 at 578-79; PTX-122 at 5311; PTX-117 at 184, 187, 192; PTX-116.0003; *see also* Davies 531:12-18, PDX-222.)

[15] Although MTPC had publicly disclosed that T-1095 had been selected for further clinical evaluation (Davies 531:12-18, 535:5-6, PDX-222), Dr. Bannister's testimony that T-1095 showed promise "in people at lowering blood sugar" is not supported by any prior art evidence (Bannister 165:12-19). In fact, Zydus did not point to any prior art clinical data for any SGLT compound demonstrating efficacy in human diabetic patients. (Davies 531:19-25.)

51. In light of this skepticism, and the availability of the numerous other "just right" categories to pursue, Zydus did not prove by clear and convincing evidence that a POSA would have focused on SGLT inhibitors.

(2) Zydus Applied Hindsight in Ignoring Numerous SGLT Compounds Having Published Activity Data

52. Even assuming, *arguendo*, that a POSA would have focused exclusively on SGLT inhibitors, Zydus did not prove by clear and convincing evidence that a POSA would have selected the '117 patent compound as a lead from among the known SGLT compounds because, *inter alia*, that compound lacked any prior art biological data.

53. In selecting a lead compound, a POSA would have considered whether known data concerning a compound's pertinent biological properties were available. (Davies 511:10-18, 518:9-519:25, 524:17-525:2, 527:25-528:7, 530:5-13, PDX-206, PDX-209.) Even Dr. Bannister agreed that "a lead compound is a prior art compound that has favorable characteristics and/or properties over other compounds that would motivate a POSA to select it as a starting point." (Bannister 289:2-7.) Specifically, a POSA would have considered an SGLT inhibitor if it demonstrated certain properties, including inducing urinary glucose excretion ***when administered orally*** and lowering blood glucose levels ***when administered orally***. (Bannister 385:20-386:6; Davies 533:11-22, 534:13-23, PDX-224.)

54. The record, however, is devoid of any prior art biological data with respect to the '117 patent compound. (Davies 541:13-543:6, 546:4-548:1, 548:19-549:6, PDX-231, PDX-234.) As Dr. Bannister acknowledged, there was no data corresponding to *in vitro* potency, *in vivo* efficacy, bioavailability, selectivity, or lack of toxicity for this compound.[16]

[16] Although the '117 patent generally describes an *in vitro* assay for SGLT2 activity, this only prophetically discloses that SGLT2 activity data "may be determined" by use of the assay.

(Bannister 289:8-20.) Nor did Dr. Bannister identify "any prior art reference making modifications to the '117 patent compound" (*id.* 292:19-22),[17] and he was "not aware of prior art information saying that [this compound] was undergoing clinical trials" (*id.* 290:8-20).

55. Further, Zydus's position that a patent without biological data can provide sufficient information for a POSA to justify the selection of a lead compound ***contradicts its own position in the District of Delaware***, where Zydus asserted that the '117 patent is invalid because it "contains no data to show a POSA that the inventor possessed or enabled [claims directed to the '117 patent compound]." (Bannister 331:23-332:10; PTX-1094 at 125.)

56. In contrast to the lack of data for the '117 patent compound in the prior art, other SGLT compounds ignored by Dr. Bannister, including MTPC's T-1095, had pharmacological efficacy data after oral administration in animal models. (*See, e.g.*, Davies 534:4-539:20, PDX-225-228; PTX-65 at [0132, 0145-0149]; PTX-68 at [0506-0510]; PTX-67 at [0384-0420]; PTX-61 at [0344-0348]; PTX-108 at 26; PTX-107 at 1550-51; PTX-122 at 5313-16.)

57. For example, Dr. Bannister admitted that "T-1095 was more thoroughly studied in the prior art than the '117 patent compound" and known to be in clinical trials. (Bannister 302:1-4, 299:19-22.) Further, Dr. Bannister admitted that "medicinal chemists were actually treating and using [T-1095] as a lead compound ***in the prior art***." (*Id.* 301:22-25.) Zydus did

---

(Davies 541:11-543:6, 639:19-640:9, 675:17-676:16, PDX-231; DTX-87 20:26-59.) With respect to selectivity, this requires SGLT1 activity data, but the '117 patent does not reference an SGLT1 assay, and Dr. Bannister did not discuss any prior art support for such an assay. (*Id.*) Zydus may attempt to demonstrate the availability of such an assay in its post-trial submission, but Zydus did not elicit any expert testimony during trial demonstrating how a POSA would have understood or used any such assay. (*See, e.g.*, Davies 678:13-679:15, 680:1-17.)

[17] The only Federal Circuit decision cited in Zydus's trial brief that applied a lead compound analysis, *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014), involved ***prior art*** evidence demonstrating that the asserted lead compound had been selected for further modification by multiple scientists and thus is inapposite. (COL ¶ 222 n.84.)

not argue, and Dr. Bannister did not show (*id.* 287:18-288:16), that the asserted claims would have been obvious if a POSA had started from T-1095—or any other prior art SGLT compound—as a lead.

(3) Dr. Bannister Did Not Establish That a POSA Would Have Disregarded O-glucosides Due to Alleged Instability

58. In attempting to justify his hindsight approach, Dr. Bannister testified that a POSA would not have selected any SGLT compound as a lead if it had an oxygen atom between the glucose portion and the rest of the molecule (referred to as "O-glucoside" compounds). Specifically, Dr. Bannister incorrectly generalized that all of the prior art O-glucosides suffered from metabolic instability issues that would disrupt activity after oral administration.[18] (*See e.g.*, Bannister 130:5-131:24.) Dr. Bannister, however, ignored that O-glucosides (such as T-1095A) were designed to be administered as "prodrugs"[19] (*e.g.*, T-1095), which Dr. Davies explained enhanced oral activity by increasing metabolic stability. (Davies 537:7-539:20, PDX-227-228; PTX-107 at 1550-51; PTX-122 at 5313-16; PTX-108 at 26.)

59. Even under Dr. Bannister's approach of focusing on a company's patenting activity,[20] the prior art demonstrates that the companies investigating SGLT compounds,

---

[18] Dr. Bannister went so far as to testify that, even if a POSA could select 100 lead compounds (which is significantly beyond the handful of compounds that a POSA would have considered), she "would select 100 C-glucosides and not a single O-glucoside." (Bannister 306:6-17.)

[19] A prodrug is an organic compound that, after administration, is metabolized by the body into an active metabolite. (*See, e.g.*, Davies 538:19-539:20, PDX-228, PDX-222; PTX-122 at 5313-16.) T-1095 is the "prodrug," while T-1095A is the "metabolite." (*See, e.g.*, PTX-116 at 1794.) As Dr. Williams recognized, apart from the clinical development of T-1095, two O-glucosides (sergliflozin and remogliflozin) also entered clinical development after 2003. (Williams 1081:11-21, 1082:6-1083:2, 1084:20-1085:8.) In fact, remogliflozin was approved in India in 2019 for treating type 2 diabetes. (Williams 1086:3-8; PTX-1099 at 1-2.)

[20] Dr. Bannister testified that "a POSA would expect that companies are improving their compounds over time[,] so more recent information would be preferable to something from years ago" (Bannister 309:21-25), and what a company "choose[s] to patent and the information they

including BMS, were also focusing on O-glucosides. (Davies 550:18-551:5.) As Dr. Davies explained, and Dr. Bannister agreed, a POSA would have known that BMS continued to pursue O-glucoside patent applications ***after*** filing the application that led to the '117 patent. (Davies 550:18-551:20, PDX-235; PTX-89; Bannister 307:11-17, 308:13-19.)

60. In fact, as Dr. Bannister confirmed, BMS described the efficacy of its O-glucosides and C-glucosides using the ***exact same*** disclosures in both sets of patents. (Bannister 308:20-309:14; PTX-340; *see also* Davies 551:6-20, PDX-236; PTX-36 at 7:22-27, 35:55-64, 35:37-39; PTX-89 at 8:29-9:3, 32:32-33:10, 32:4-7.) As such, a POSA would not have been able to distinguish between BMS's C-glucosides and O-glucosides. (Davies 551:9-20.) Even Dr. Bannister had to admit that a POSA would have known that BMS "didn't put all of their eggs in the aryl C-glucoside basket." (Bannister 311:8-22.)

(4) Dr. Bannister Did Not Establish That a POSA Would Have Viewed C-glucosides as Having Improved Activity

61. Dr. Bannister also testified that, based on Link, US '674, and the BMS '126 and '117 patents, a POSA would have understood that C-glucosides had improved activity after oral administration compared to O-glucosides. (*See, e.g.*, Bannister 141:15-144:3.) ***None*** of these references, however, disclosed activity data after oral administration, let alone demonstrated improved activity compared to O-glucosides.

62. As Dr. Davies explained, Link disclosed *in vitro* experiments that could not assess oral activity.[21] (Davies 544:24-545:17, PDX-233; PTX-112 at .0003, .0005 n.16.) Moreover, the results showed that the tested C-glucosides were much weaker than their corresponding

---

provide can certainly be reflective of the state of their research and what they considered to be important" (*id.* 310:12-25).

[21] Despite alleging that Link's C-glucosides were "presumably stable," Dr. Bannister acknowledged that the article "doesn't describe the[ir] stability . . . ." (Bannister 136:16-21.)

O-glucosides, which led the authors of Link to conclude that the O-glucoside linkage was important to SGLT-inhibition activity. (*Id.*)

63. Regarding US '674, Dr. Davies explained that, although the patent application disclosed results of an *in vivo* experiment, it was based on "i.p." (intraperitoneal) administration, which does ***not*** provide a measure of activity after oral administration.[22] (Davies 543:7-544:15, PDX-232; PTX-58 at .0017.) Moreover, because US '674 did not compare any of its C-glucoside compounds to O-glucosides, a POSA could not have known whether those compounds were "in the ballpark" of T-1095A, as Dr. Bannister baselessly alleged. (Bannister 135:18-21.)[23]

64. Similarly, despite Dr. Bannister's unsupported testimony that a POSA would have viewed the '126 and '117 patents as a "breakthrough" (*id.* 143:2-144:3), BMS's O-glucoside patents describe those compounds in the exact same way. (*See supra* Section III.B.3.) Regardless, Dr. Bannister conceded that "no prior-art reference . . . calls BMS's C-glucoside work a breakthrough." (Bannister 305:18-24.) Notably, Zydus is arguing in the District of Delaware that the ***same BMS C-glucoside patents*** were not a "breakthrough," but instead ***obvious*** over the prior art. (Bannister 326:8-327:22; PTX-1094 at 1.) As explained in Section III.C.1.b this is not the only example of Zydus taking one position before this Court, and the exact opposite before another.

---

[22] Intraperitoneal administration is an injection into the body cavity that bypasses key metabolic processes implicated in oral administration, such as those occurring in the gastrointestinal tract. (Davies 543:7-544:15, PDX-232; PTX-58 at .0017; *see also* Williams 1091:2-14 (agreeing that intraperitoneal administration "bypasses the gastrointestinal tract").)

[23] Dr. Bannister admitted that he did not know "how the[] compound[s] w[ere] administered in [US] '674 . . . ." (Bannister 138:24-25.)

65. As Dr. Davies explained, a POSA could not have compared the efficacy of the prior art SGLT compounds to the '117 patent compound because there was no biological data disclosed in the prior art with respect to the latter compound. (Davies 541:13-543:6, 546:4-548:1, 548:19-549:6, PDX-231, PDX-234.) Dr. Bannister agreed. (Bannister 350:1-10.)

(5) Dr. Bannister's Testimony That the '117 Patent Compound Was BMS's "Best" C-glucoside Is Inconsistent with His Prior Opinion and Does Not Justify Selecting It as a Lead Compound

66. Dr. Bannister testified that a POSA would have believed that the '117 patent compound was the "best" BMS C-glucoside because it was the only compound disclosed in the '117 patent. (Bannister 321:1-4, 322:9-15.) As an initial matter, this opinion is a departure from the opinions Dr. Bannister disclosed during expert discovery, where he claimed that Example 10 of the '126 patent (another BMS C-glucoside) would also have been selected as a lead compound.[24] Dr. Bannister even acknowledged that "[i]t's not clear," as between the '117 patent compound and Example 10, "which of them has more favorable characteristics or properties." (*Id.* 292:23-293:12.) Dr. Bannister also admitted that "there were certainly other compounds that had some appeal" as leads, including Example 1 of the '126 patent. (*Id.* 297:17-298:7.)

67. These shifting positions are emblematic of Dr. Bannister's frivolous, hindsight-based arguments. In any event, Dr. Bannister's argument that the '117 patent disclosed a single compound could ***at most*** demonstrate only that the '117 patent compound was ***BMS's*** best

[24] Zydus did not allege that a POSA would have identified the '117 patent compound as a lead in its June 5 and 6, 2017 Paragraph IV Notice Letters challenging the validity of the patents-in-suit, and instead focused only on the Example 10 compound. Since its original Paragraph IV Notice Letters in the summer of 2017, until at least the submission of its Corrected Proposed Findings of Fact and Conclusions of Law on May 29, 2020 (D.I. 170 at 168-173; *see also* D.I. 165 at 16), Zydus asserted Example 10 as a lead compound. Zydus, however, did not present evidence of Example 10 as a potential lead compound at trial. As such, the Court held that Zydus had withdrawn its reliance on Example 10 as a lead compound in its obviousness case and granted judgment as a matter of law on that issue. (Court 494:9-13.)

C-glucoside compound among those disclosed in the '126 patent. As Dr. Davies explained, this falls far short of an adequate justification for a POSA to have selected it over all of the other more promising SGLT compounds that were being researched by other companies and had biological data, as discussed above. (*See, e.g.*, Davies 534:4-539:20; *supra* Section III.B.2.)

68. Dr. Bannister attempted to justify his selection by claiming, for the first time at trial, that he "almost never" comes across a one-compound patent. (Bannister 147:6-8.) After hearing this new opinion, however, Dr. Davies handily identified 20 examples that dispelled Dr. Bannister's testimony. (Davies 712:10-716:21; *see, e.g.*, PTX-1095; PTX-1096; PTX-1097; PTX-1098.) In fact, Dr. Bannister's testimony that a POSA would have selected a lead compound based on such information is not supported even by his own "Nogrady" reference, which he admitted did not list "looking for patents that claim just one compound" (much less patents in general) as one of the "several well-tested methods for uncovering or identifying lead compounds." (Bannister 294:16-295:13; *see generally* DTX-202.)

69. Dr. Bannister also testified that the scale of synthesis disclosed in the '117 patent would have allegedly influenced a POSA. (Bannister 152:6-154:9.) As Dr. Davies explained, however, the '117 patent disclosed the synthesis of only 20.4 grams, which was not even enough to progress into toxicology studies or clinical development.[25] (Davies 549:21-24, 550:10-17.)

70. In fact, Dr. Bannister admitted that such multigram synthesis would have conveyed simply that a compound "was ***moving toward*** *in vivo* studies." (Bannister 303:11-24.) This potential inference would not have prompted a POSA to select the '117 patent compound over the many other potential lead compounds identified above, including those that were

[25] Other uses for the synthesis of multigram amounts could include, for example, making derivative compounds, performing crystallization studies, or conducting preliminary animal tests. (Davies 550:1-9.)

already reported to have promising *in vivo* data in the prior art. (Davies 549:21-550:17, 551:24-552:8, PDX-237.)

71. In sum, Zydus's lead compound analysis is unsupported by the disclosures in the prior art and, instead, is driven entirely by hindsight. (COL ¶¶ 221-22.)

C. Zydus Did Not Prove That a POSA, Without Hindsight, Would Have Been Motivated to Make All Four of Its Alleged Changes to the '117 Patent Compound

72. Even assuming that a POSA would have selected the '117 patent compound as a lead compound (which she would not have), Zydus did not prove by clear and convincing evidence that a POSA would have then been motivated to make the four significant structural modifications Zydus suggests to arrive at the compound now known as canagliflozin.[26] These four significant structural modifications are as follows:

1. Changing the 4-chloro group of the "A Ring" to a 4-methyl group;
2. Changing the phenyl "B Ring" to a thiophene ring having a specific, "2,5" orientation;
3. Changing the 4-ethoxy group to a new phenyl ring; ***and***
4. Changing the 4-hydrogen of the new phenyl ring to a 4-fluoro group.

(Davies 555:5-557:2, PDX-239; Bannister 315:19-316:1 (agreeing that, in his expert report, he "listed four changes that [he] allege[d] would be made to the '117 patent compound").)

73. Zydus's obviousness defense is premised on the POSA making all four of these changes simultaneously, while not making any other changes to the molecule,[27] which conflicts

[26] Both Zydus and Dr. Bannister confirmed that a POSA would not have started making modifications from Dr. Bannister's alleged "BMS scaffold." (Bannister 196:25-201:13.) Instead, a POSA would start from a properly established lead compound. (*Id.*; *see also* COL ¶¶ 217, 221.)

[27] As discussed in Section III.C.1-4 and Section III.D below, Zydus also did not prove that a POSA would have been motivated to make any one of these changes—let alone ***all*** of them at

with Dr. Bannister's admission that drug discovery typically proceeds with "[o]ne change at a time" as part of a "highly iterative process." (Bannister 315:2-12; *see also id.* 316:8-17 (conceding that a POSA "would tend to [make a] fewer number of changes at once").) This is one of numerous fundamental flaws in Zydus's motivation analysis.

74. Zydus's obviousness defense is also premised on the POSA changing both structural features of the compound that Zydus argues would have been the ***very basis for selecting it*** as a lead in the first place. (COL ¶ 225.) As Dr. Davies explained, a POSA would not have acted in such an arbitrary and counterintuitive manner. (Davies 586:25-587:15, PDX-259.) Here, Dr. Bannister asserted that a POSA would have chosen the '117 patent compound as a lead because BMS's C-glucoside patents allegedly "tell[] you that that R^1 . . . chloro . . . and R^4, ethoxy, is their best compound."[28] (Bannister 172:4-173:15, Bannister Slides 37-38; *see also* Bannister 319:1-21, 320:13-321:4 (asserting that "the structure of the '117 patent compound was quite important").) As even Dr. Bannister conceded, the POSA "would seek to retain" substituents that are understood to provide such "highly favorable biological properties." (Bannister 321:5-322:5.)

75. Even ignoring this glaring inconsistency, as demonstrated at trial and explained below, Zydus's proposed changes are self-contradictory, lack prior art support, and are even ***contradicted by the very BMS patents*** on which Zydus alleges a POSA would have focused.

---

the ***same time***—***and*** while maintaining all other aspects of the '117 patent compound. (COL ¶¶ 230-31.) A failure of proof by Zydus on just one of these issues is sufficient to reject its obviousness defense; Zydus has not come close to proving any of them by clear and convincing evidence.

[28] The "R^1" refers to the 4-chloro group (*i.e.*, Zydus's first alleged change), and the "R^4" refers to the 4-ethoxy group (*i.e.*, Zydus's third alleged change).

(1) *First Alleged Change*: Zydus Did Not Prove That a POSA Would Have Been Motivated to Change the 4-Chloro of the '117 Patent Compound to a 4-Methyl

a. There Was No Motivation to Change the 4-Chloro of the '117 Patent Compound

76. Despite initially asserting that the 4-chloro group of the '117 patent compound would have been changed to a 4-methyl group to "design around" the BMS patents (Bannister 317:10-14), Dr. Bannister admitted that this position is flawed because this proposed change actually falls within the scope of BMS '126 patent (Bannister 317:15-19; *see also* Davies 558:18-559:22, PDX-241; PTX-36 at 8:43-62). Accordingly, even if Zydus's flawed "design around" approach was accepted,[29] the POSA would not have been motivated to make this proposed change because it would not have advanced that goal.

77. With this mistake exposed, Dr. Bannister resorted to testifying that the POSA would have been motivated to make this change[30] based on an alleged understanding that 4-chloro and 4-methyl were "roughly equally valid options" based on "what is most preferred in the '126 patent." (Bannister 322:16-21, 323:11-25; *see also id.* 317:1-9 (asserting that these groups were "likely to be interchangeable"); COL ¶ 224.)

78. This is not a credible motivation, however, because it does not promote what Dr. Bannister acknowledged would be the "typical goal" of the POSA—namely, "to try and ***improve*** th[e] starting compound in some regard." (Bannister 314:23-315:4; *see also supra* Section III.A.) As Dr. Bannister admitted, a POSA would not have "expected that changing

[29] As explained in Section III.A above, Zydus did not prove that a POSA would have been motivated to "design around" the BMS patents.

[30] Dr. Bannister attempted to minimize this proposed change by characterizing it as a "choice" (*see, e.g.*, Bannister 192:9-193:9), which was contrary to his expert report (*id.* 315:19-22, 387:20-388:21).

the 4-chloro of the '117 patent compound to a 4-methyl would improve any property of that compound." (Bannister 323:6-10.)

b. Zydus Has Acknowledged That the Prior Art Actually Taught Away from Its Proposed Chloro-to-Methyl Change

79. As Dr. Davies established, Dr. Bannister's own prior art ***pointed away*** from his proposed chloro-to-methyl change. Specifically, Patani taught the opposite change—*i.e.*, changing a methyl to a chloro—because of methyl's "ability to alter the metabolism" by "provid[ing] a site [that] is susceptible to metabolic degradation," which would result in metabolic instability.[31] (Davies 559:23-561:2, PDX-242; DTX-208 at 3153-54; *see also* Bannister 325:20-23 (agreeing that metabolic degradation "means that the metabolic stability of the compound is adversely affected").)

80. In fact, Dr. Bannister's position is flatly contradicted by ***Zydus's own interpretation of Patani in a different, pending litigation*** in the District of Delaware. There, Zydus asserted, based on the same Patani reference, "that ***chlorine would be preferable to methyl*** because 'of its ability to prevent the metabolism of the compound caused by the presence of the methyl group.'" (Bannister 328:23-330:3 (agreeing that, "in the Delaware case, Zydus is arguing that chlorine would be preferable to methyl"); PTX-1094 at 92.) Dr. Bannister's concession at trial that "there are some differences" between the positions Zydus is taking regarding Patani before two different courts is an understatement. (Bannister 330:4-14.)

[31] By contrast, Dr. Bannister alleges that a POSA would have made other changes precisely to address metabolic instability concerns, which is one of many inconsistencies between Zydus's obviousness allegations. (*Infra* Section III.C.4.)

81. In sum, Zydus did not demonstrate by clear and convincing evidence that a POSA would have been motivated to change the 4-chloro of the '117 patent compound to a 4-methyl. (COL ¶¶ 224, 226.)

(2) *Second Alleged Change*: Zydus Did Not Prove That a POSA Would Have Been Motivated to Change the Distal Phenyl of the '117 Patent Compound to a Thiophene

82. Dr. Bannister testified that, at the same time the above-mentioned "choice" was being considered, a POSA would have also been motivated to change the phenyl B Ring of the '117 patent compound to a thiophene ring in a specific orientation[32] to "design around" BMS's patents. (Bannister 175:4-176:6, 333:22-334:9, Bannister Slide 40; *see also* Davies 564:21-565:24, 557:3-23, PDX-244.) Again, the evidence at trial demonstrated that a POSA would not have had such a motivation. (*See supra* Section III.A; *see also* COL ¶ 223.) This is particularly true in light of Dr. Bannister's concession that this second proposed modification would not result in "any sort of improvement in the properties of the '117 patent compound" (Bannister 337:23-338:2), which conflicts with the POSA's goal of trying "to develop a better or improved medicine for treatment of Type 2 diabetes" (*see supra* Section III.A).

83. Even if Zydus did prove that a POSA would have been motivated to "design around" the BMS patents, however, Zydus's proposed change is still unsupported by the evidence at trial for the reasons set forth below.

[32] This specific orientation is referred to as a "2,5-di-substituted thiophene." (Davies 565:3-24.) As discussed in more detail below, a thiophene can be mono-substituted (*i.e.*, have only one connection), di-substituted in a different orientation (*e.g.*, a "2,3" orientation), or even have more than two connections to other items (*e.g.*, be tri-substituted).

a. BMS's "Guidance" Taught Away from Changing the Phenyl B Ring of Its C-glucoside SGLT Inhibitors

84. Dr. Bannister relied heavily on the '126 patent during his testimony, arguing that this BMS patent was a "breakthrough" (Bannister 143:2-144:3) and that a POSA "would anticipate that [the C-glucosides disclosed in that patent] could be really important" (*id.* 350:1-10). As such, Dr. Bannister opined that a POSA would "keep as much as what BMS teaches to be essential intact." (*Id.* 351:21-352:1; *see also id.* 350:24-351:20 (asserting that a modification would be "much lower in priority" if it was "not the substitution pattern that BMS clearly identifies as most preferred").)

85. As Drs. Bannister and Davies agreed, a phenyl ring is present at the B Ring in every one of the compounds disclosed in the '126 patent, and BMS did not permit any other group besides phenyl at that location. (*Id.* 352:12-353:18; Davies 566:1-567:10, 568:19-24, PDX-245; PTX-36 at 6:22-37.) In fact, Dr. Bannister admitted that the '126 patent "permits ring structures other than phenyl to be used in areas of the compound besides the B ring" (Bannister 353:19-354:1), yet "***discloses that the B ring is limited only to phenyl***" (*id.* 353:16-18) (emphasis added).

86. Dr. Bannister referred to this teaching as BMS's "guidance" (*id.* 353:5-11), and presumed that BMS was "attempting to make better compounds, including by focusing on the B ring." (*Id.* 348:23-349:3, 349:23-25.) As Dr. Davies explained, a POSA would have understood BMS's decision to cover only phenyl in the B Ring as intentional because BMS demonstrated that it knew how to claim B Ring structures other than phenyl in its other SGLT patents. (Davies 567:11-568:18, PDX-246-247; PTX-36 at 6:2-38; PTX-59 at [0030]-[0033] (permitting a large number of heteroaryls at the B Ring); DTX-180 at 63 (equivalent to US '315).) Dr. Bannister agreed with Dr. Davies' explanation. (Bannister 356:24-357:3

(agreeing that "BMS knew how to claim alternative ring structures to phenyl when it wanted to do so . . . [i]ncluding at the B ring")).

87. Accordingly, a POSA following the teachings of BMS's '126 patent would not have changed the phenyl B Ring because she would have understood that this ring structure was preserved for a reason. (Davies 566:1-567:10, PDX-245; *see also* COL ¶ 227.)

b. Zydus's General "Bioisosterism" References Do Not Support Its Alleged Change from Phenyl to Thiophene

88. Dr. Bannister's alleged change of phenyl to thiophene does not have any support in the relevant prior art. (Bannister 336:5-336:20 (testifying that he did not recall "any prior art reference showing that the replacement of a phenyl ring with a thiophene in an SGLT compound would maintain or increase efficacy").) Implicitly recognizing this, Dr. Bannister retreated to relying upon the concept of "bioisosterism." (*Id.* 337:15-18.) But Dr. Bannister admitted that none of his "bioisosterism" references actually involved the molecular structures at issue in this case, *i.e.*, SGLT compounds. (*See, e.g.*, *id.* 336:5-20, 392:22-25.) The Federal Circuit has routinely rejected such abstract bioisosterism arguments as a basis for obviousness (COL ¶ 227),[33] and the result should be no different here.

[33] Dr. Bannister replaced Zydus's original medicinal chemistry expert, Dr. Clayton Heathcock, after Dr. Heathcock's opinions regarding bioisosterism (which are virtually identical to the ones offered by Dr. Bannister here) were rejected in the District of Delaware. (Bannister 342:1-19; D.I. 166 at 22 n.22). Interestingly, the District of Delaware relied on the testimony of Dr. William Roush to reject Dr. Heathcock's bioisosterism opinions. *See UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 543 (D. Del. 2016) (relying on Dr. Roush's testimony that "a POSA would not have been able to predict the effect of a bioisosteric substitution" in rejecting Dr. Heathcock's bioisosterism opinions); *see also Mylan Pharm. Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366, 1376 (Fed. Cir. 2019) (affirming rejection of Dr. Heathcock's bioisosterism opinions in favor of Dr. Roush's testimony). As Dr. Bannister admitted, he "generally trust[s] Dr. Roush's judgment in matters of chemistry," as he is "a very capable chemist" with "substantial" knowledge in chemistry. (Bannister 342:20-343:7.)

89. As Dr. Bannister's Sheridan reference (which, like Patani, did not address any SGLT molecules) makes clear, bioisosterism is not a panacea for every situation; rather, it depends on numerous factors, such as the desired bioactivity and the particular position of the molecule being evaluated. (Davies 569:23-572:5, PDX-248-249; DTX-210 at 103 ("If M1 and M2 have similar biological activities, the claim is often made that X1 and X2 are bioisosteres . . . . This may not be generally true . . . [a]ll that can be inferred is that X1 might be equivalent to X2 at that one position and only for that bioactivity").)[34]

90. Instead, a POSA would understand a particular substitution as "bioisosteric" only in hindsight because there are no hard-and-fast rules that can reasonably predict (especially without reliable data in the context being studied) that the change from one substituent to an alleged "bioisostere" in one series of compounds will result in similar, let alone improved, biological effects in a different series of compounds. (Davies 569:23-572:5, PDX-248-249.)[35]

91. Dr. Davies provided examples of this during his testimony, such as the alleged "bioisosteric" modification of changing the oxygen in $H_2\mathbf{O}$ to sulfur in $H_2\mathbf{S}$, which results in a molecule of water becoming a molecule that is toxic in large quantities. (Davies 570:18-571:7, PDX-249; *see also* Davies: 571:8-572:5; DTX-208 at 3159.) Dr. Davies also showed (in contrast to Dr. Bannister) that examples of changes Dr. Bannister characterized as allegedly "bioisosteric" reduced efficacy in prior art SGLT compounds, demonstrating the overextension

[34] Although Dr. Bannister referenced the non-prior art Lima reference in support of his alleged motivation opinions, Lima acknowledges that a single bioisosteric replacement can "dramatically alter the physiochemical properties of substances and, therefore, their activities." (DTX-199 at 25 (dated 2005).)

[35] Dr. Bannister also ignored the warning in Sheridan that its activity data "may not always be reliable" (DTX-210 at 108), and did not perform any investigation into that unreliability (Bannister 345:5-20.) In fact, Dr. Bannister did not even know how Sheridan used the activity data to determine whether a replacement resulted in the molecule maintaining, losing, or gaining activity. (*Id.* 345:21-346:15.)

of Dr. Bannister's argument. (*See, e.g.*, Davies 572:6-575:16, PDX-250; PTX-67 at [0167], [0176], [0234].)

92. Even more problematic, Dr. Bannister did not provide any prior art support for the specific phenyl-to-thiophene substitution that he testified a POSA would have made. As Dr. Davies explained, Dr. Bannister testified that a POSA would have changed the di-substituted phenyl in the '117 patent compound to a ***di***-substituted thiophene,[36] but his cited examples in Sheridan discuss only changing a mono-substituted phenyl to a ***mono***-substituted thiophene. (Davies 580:6-18, 582:5-11, PDX-256; DTX-210 at 106.) As Dr. Bannister admitted, Sheridan "does not make a pairwise correlation of a . . . disubstituted phenyl with 2,5-disubstituted thiophene." (Bannister 346:16-347-10.)

c. The Prior Art as a Whole Taught Away from Using Thiophene

93. Dr. Bannister testified that "bioisosteric" changes—including phenyl to thiophene—would be expected to retain activity. (*See, e.g.*, *id.* 183:18-184:25, 189:7-12, 196:2-14; s*ee also* 337:15-22.) Dr. Bannister did not provide any prior art examples of thiophene being considered a bioisostere in the SGLT context (much less benefiting an SGLT inhibitor). Moreover, Dr. Bannister admitted that, "[i]n the only three C-glucoside prior art papers" he discussed during his testimony (US '674, and BMS's '126 and '117 patents), "none of them describe" "a C-glucoside SGLT inhibitor that contains a thiophene ring at any location." (Bannister 336:21-25; *see also id.* 344:4-8 (admitting that thiophene was a

[36] As Dr. Davies explained, this modification would rotate the entire right-hand portion of the molecule by roughly 30 degrees. (Davies 581:7-10.) Given the potential consequences of this significant rotation on the molecule's biological properties, introducing a di-substituted thiophene would not have been considered a "bioisosteric" change. (*Id.* 580:7-10, 581:11-23, 582:12-18, PDX-257; *see also supra* Section III.C.2.b.)

"new thing" that "does not appear in the C-glucoside prior art").) In fact, Dr. Bannister did not identify a ***single example anywhere in the SGLT prior art*** of the specific 2, 5-disubstitued thiophene he asserts a POSA would have used here. (*Id.* 337:11-14.)

94. Instead, Dr. Bannister reviewed US '315 and plucked out Example 68, which was the only one of 101 exemplary ***O-glucoside*** SGLT inhibitors disclosed in that patent containing a thiophene ring anywhere in its structure. (PTX-59 at [0271-0321]; Bannister 344:9-18; *see also id.* 343:16-344:8 (agreeing that a POSA would have relied on the O-glucoside prior art "a little less" when modifying a C-glucoside).) Example 68, however, does not fall within any preferred genus of the disclosed compounds (PTX-59 at [0054]-[0064]), signaling that it was not among the desired compounds of that patent.[37] (*See, e.g.*, Davies 588:12-589:6.)

95. This is consistent with examples in the prior art showing detrimental effects when using thiophene. Dr. Davies provided specific examples of phenyl-to-thiophene substitutions reducing the efficacy of SGLT compounds, which is the opposite of a "bioisostere." Specifically, Dr. Davies provided examples from Dr. Bannister's own prior art references, Hongu and US '143. In Hongu, Dr. Davies explained that the impact of changing a phenyl (compound 7) to a thiophene (compound 21) at the B Ring location of a SGLT compound reduced by four-fold the *in vivo* urinary glucose excretion activity after oral administration. (Davies 573:17-574:16, PDX-251; PTX-108 at 25-26.)

[37] Even if a POSA would have ignored these other options and focused on Example 68 of US '315 (which Dr. Bannister did not establish), it would not have resulted in canagliflozin. In particular, that example supports at most introducing a mono-substituted 3-thiophene. (Davies 567:13-23, PDX-246; PTX-59 at 3, 25.) In contrast, canagliflozin contains a thiophene in a different orientation (*i.e.*, a 2-thiophene) as well as a different substitution pattern (di-substituted at the 2- and 5- positions). (*Id.*; *see also* Davies 564:25-565:14.)

96. With respect to Dr. Bannister's US '143 reference, Dr. Davies showed the three- to five-fold worsening of *in vitro* activity from phenyl (Example 56) to thiophene (Examples 5 and 6). (Davies 574:17-575:16, PDX-252; PTX-64 at [0025], [0167].) These examples belie Dr. Bannister's assertion that a POSA would have viewed thiophene as a desirable option in an SGLT compound in light of the prior art, and further undermine his reliance on abstract "bioisosteric replacement" assertions.

97. In sum, Zydus did not demonstrate by clear and convincing evidence that a POSA would have been motivated to change the phenyl B Ring of the '117 patent to a thiophene, let alone in the specific orientation and substitution pattern present in canagliflozin. (COL ¶¶ 227, 231.)

(3) *Third Alleged Change*: Zydus Did Not Prove That a POSA Would Have Been Motivated to Change the 4-Ethoxy of the '117 Patent Compound to a Phenyl

a. A POSA Would Not Continue Making Modifications

98. Even assuming a POSA would have been motivated to design around BMS's patents (she would not have been), Drs. Davies and Bannister agreed that this would have been accomplished by the thiophene modification just discussed. (Davies 583:25-584:13; Bannister 357:18-21.) As Dr. Bannister testified, "a POSA would want to keep as much as what BMS teaches to be essential intact" after "skirt[ing] their patent." (Bannister 361:2-8.) "[I]n other words," as Dr. Bannister put it, a POSA "would try to change as little as you could get away with." (*Id.*) According to his own analysis, Dr. Bannister failed to show that a POSA would have been motivated to continue making changes after satisfying this alleged goal.[38]

[38] *See* Bannister 358:1-360:21 (admitting that, "in terms of seeking structures," a POSA's "motivation would be lower[ed and] maybe you have arrived at your goals" to the extent the

99. This is particularly true given that, as Drs. Davies and Bannister agreed, a POSA would test each change to a lead compound so that she "can isolate the biological activity for that one specific change." (Bannister 315:9-18; *see also* Davies 555:23-556:1, 600:3-14.) As both experts also agreed, no data—from the prior art or otherwise—relating to the proposed phenyl-to-thiophene change exists in the record. (Bannister 361:19-362:11; Davies 586:1-3, PDX-257.) Absent such data showing the effects of the changes just made, a POSA would not have been motivated to continue making further changes, which provides an independent reason to reject Zydus's obviousness defense. (COL ¶ 230.)

b. Dr. Bannister's Alleged "Toxicity" Motivation Cannot Be Reconciled with His Other Opinions and Is, in Any Event, Unsupported

100. Even assuming further changes would have been considered by a POSA, Dr. Bannister admitted that replacing the 4-ethoxy of the '117 patent compound with a new phenyl ring would not "design around" BMS's patents. (Bannister 357:14-17.) Dr. Bannister further admitted that this proposed change would have been understood by a POSA as neither bioisosteric (Bannister 340:2-341:1; *see also* Davies 587:16-588:5, PDX-260; COL ¶ 228 n.86) nor one that would result in any improved biological properties (Bannister 362:12-16). In fact, as Dr. Davies explained, a POSA would not even have expected this type of significant modification to maintain, much less improve, efficacy because of the dramatically different properties of these groups. (Davies 586:4-24 (discussing differences in size, electronics (*e.g.*, polarity), and lipophilicity), PDX-258.) As such, none of Dr. Bannister's previous alleged motivations for making modifications applies to his proposed ethoxy-to-phenyl change.

---

alleged thiophene substitution was made); *see also* Davies 582:19-584:13, 690:17-691:1, 691:9-17, PDX-257.)

101. For this dramatic change—*i.e.*, the reintroduction of the phenyl ring that was just replaced—Dr. Bannister concocted yet another alleged motivation: He testified that a POSA would have made this change to solve an alleged "toxicity" problem that was ***just created*** by his phenyl-to-thiophene B Ring substitution. (Bannister 243:2-6, 243:17-24; Davies 582:19-583:1, PDX-257.) In other words, after alleging that a POSA would have been motivated to change the phenyl to a thiophene based on bioisosterism principles, Dr. Bannister then testified that this supposedly "bioisosteric" change would have actually raised a toxicity concern. (Bannister 241:24-243:6.) This counterintuitive approach underscores Dr. Bannister's significantly flawed obviousness analysis.

102. It makes no sense for a POSA to have made a change (*i.e.*, phenyl to thiophene) that creates a new, supposedly expected problem. (Davies 583:2-15.) And, even worse, such a "problem" was not shown to actually exist: Dr. Bannister provided ***no prior art support*** for his alleged toxicity concern.[39] (Bannister 361:21-362:11; Davies 583:17-24.) Thus, either Dr. Bannister's proposed phenyl-to-thiophene change would not have been made by a POSA due to toxicity concerns, or there would be no motivation to make further substitutions according to Dr. Bannister's analysis. Either way, Zydus's obviousness defense is irreconcilably flawed.

c. The Prior Art Does Not Provide Any Motivation to Add a Third Phenyl Ring

103. Irrespective of the above, Dr. Bannister's motivation analysis should also be rejected because the evidence at trial showed that a POSA would have understood that a third phenyl ring would not have been desirable in a SGLT inhibitor compound. (Davies

[39] Dr. Bannister did not prove that a POSA would have attempted to solve a problem without confirming that it existed in the first place—nor would she. (Davies 555:23-556:1, 583:2-583:24, 584:14-586:3, 600:7-14, 608:8-22, PDX-206, PDX-257; *see also* COL ¶ 228.)

588:11-595:5, PDX-261-262; PTX-36 at 8:35-62, 22:46-67, 25:30-26:17, 64:6-67; PTX-59 at [0056]-[0063], [0321].)

104. Dr. Bannister relied on Example 26 of the '126 patent, which has a third phenyl ring (as well as phenyl A and B Rings), in an effort to support his third proposed change. (Bannister 365:18-367:21; Davies 588:11-590:5, PDX-261; PTX-36 at 8:35-62, 64:6-67.) Example 26, however, neither falls within the "more" or "most preferred" genus of the '126 patent nor is a specifically claimed compound. (Bannister 368:22-369:2; Davies 588:11-590:5, PDX-261; PTX-36 at 8:35-62, 64:6-67.)[40]

105. Dr. Bannister recognized that such a modification would be "much lower in priority" given that it was "not the substitution pattern that BMS clearly identifies as most preferred." (Bannister 350:24-351:20; *see also* 369:3-24 (testifying that "[t]here is no indication [in the '126 patent] that [a third ring] would be advantageous" or "deleterious").) Indeed, the "most preferred" genus provided billions of options, and Dr. Bannister did not prove that a POSA would have searched beyond this large group of compounds into less preferred options. (Davies 588:11-590:5, PDX-261; PTX-36 at 8:35-62, 64:6-67.)[41]

106. In sum, Zydus did not demonstrate by clear and convincing evidence that a POSA would have been motivated to change the 4-ethoxy of the '117 patent compound to a new phenyl ring. (COL ¶¶ 228, 230-31.)

---

[40] Dr. Bannister also relied on Example 11 from US '315. (Bannister 362:18-363:2.) As with Example 26 of the '126 patent, however, Example 11 is not among the "most preferred" compounds of its application. (Bannister 363:14-364:6; DTX-173 at [0060]-[0063]; *see also* Davies 590:6-22, PDX-262; PTX-59 at [0056]-[0063], [0321].)

[41] Dr. Bannister also briefly discussed the benzofuran group in T-1095A, which he vaguely referred to as "a B/C fused ring." (Bannister 240:7-241:5.) As Dr. Davies explained, however, this benzofuran group represents only a single substituent (not two, separated ring components), and would not have motivated a POSA to make a compound having a three-ring structure. (Davies 595:6-597:9; PTX-36 at 25:30-64.)

(4) *Fourth Alleged Change*: Zydus Did Not Prove That a POSA Would Have Been Motivated to Change the 4-Hydrogen of the '117 Patent Compound to a 4-Fluoro

a. A POSA Would Not Continue Making Even More Changes

107. Even assuming a POSA would have been motivated to add a new distal phenyl to the '117 patent compound (she would not have), Dr. Bannister did not prove that a POSA would have been motivated to continue making yet more changes. (Davies 555:14-556:1, 584:18-585:25, 599:22-600:14, PDX-206; COL ¶ 230.)

108. Before trial, Zydus asserted that a fluorine substitution on the new third phenyl ring would have been made to address metabolic stability concerns. (D.I. 170 at 150, 153-154.) At trial, however, Dr. Bannister testified that a POSA would have made this modification "whether [metabolic stability] was an issue or not." (Bannister 246:1-6.) Instead, in an attempt to justify his argument that a POSA would have continued to modify the compound that resulted from his (now three) previous changes, Dr. Bannister baldly asserted that "people add fluorines to phenyl groups all the time"[42] (*id.* 223:5), and that fluorine is a "really good thing to try because it so often improves the activity" (*id.* 224:10-12).

109. Dr. Bannister, however, had already opined that a POSA would have been "stunned" to find that the new compound resulting from his previous three changes was anything but a potent SGLT2 inhibitor. (*Id.* 222:15-223:1, 367:1-10.) As a result, a POSA would not had been motivated to make even more changes for the sake of improving the activity of a compound that was already believed to be potent.

[42] Dr. Bannister based his opinion on the assertion that his students do "fluorine scans" on a "daily basis," which involves placing fluorine "everywhere [they] can" on the molecule. (Bannister 223:6-225:11.) Dr. Bannister, however, did not provide any prior art support regarding the allegedly common use of "fluorine scans" during the relevant time period. (*Id.* 223:19-21.)

b. The Prior Art Did Not Provide Any Motivation to Fluorinate a Third Ring

110. Regardless, Dr. Bannister's own references refute his new "improved activity" theory. As Dr. Davies explained, a POSA would have understood Patani to warn against substituting a fluorine for a hydrogen—the very change for which Dr. Bannister advocates—because it can cause "major differences in pharmacological properties" of the resulting molecule. (Davies 598:10-599:7, PDX-264; DTX-208 at 3149.)

111. Moreover, as discussed above, Dr. Bannister asserts that a POSA would keep as much of what the BMS '126 patent teaches intact and place lower priority on substitutions outside those teachings. (*See supra* Section III.C.2.a.) Yet, ***none*** of the '126 patent examples support Dr. Bannister's proposed 4-fluoro addition to his newly added third phenyl ring. Example 26—the only example of a three-ring compound in the entire patent—did not possess a fluorine group. (Davies 599:13-601:3, PDX-265; PTX-36 at 64:43; *see also* Bannister 372:16-373:15.) And the '126 patent teaches that the 4-fluoro substitution present in Example 64, is not covered by the patent's most preferred genus (Bannister 370:17-371:13, PTX-36 at 8:43-62), which would have told a POSA that a fluorine in such a position may not improve the molecule (Davies 601:4-23, PDX-266; PTX-36 at 64:20-65:60 (Tables 1-2)).

112. In sum, Zydus did not demonstrate by clear and convincing evidence that a POSA would have been motivated to change the 4-hydrogen of the newly added phenyl ring to a 4-fluoro. (COL ¶¶ 229, 230-31.)

D. A POSA Would Have Considered Numerous Other Potential Modifications to the '117 Patent Compound under Dr. Bannister's Analysis

113. Applying the rationales offered by Dr. Bannister for his alleged motivations results in countless other potential modifications that Dr. Bannister himself did not consider or address. This is a product of what even Dr. Bannister conceded to be a hindsight approach:

He identified his selected modifications by reviewing the prior art with the structural features of canagliflozin in mind (Bannister at 279:8-21) and looked to see "whether there was support or not" for these features (*id.* 279:22-280:4; *see also id.* 382:15-21).

114. In other words, as Dr. Bannister described it during his testimony, he focused on whether or not "the dots between [the '117 patent compound] and canagliflozin" could be "connect[ed]," and, in doing so, ignored numerous other potential options at various portions of his alleged lead compound. (*Id.* 377:22-378:8.) Reviewing those options reveals the enormous number of possibilities that a POSA would have had to consider, only one of which is canagliflozin.

(1) Dr. Bannister's Alleged Motivations Provide Countless Other Potential Modifications, Which He Simply Ignores

115. **First Alleged Change:** Even if a POSA accepted that chloro and methyl are "roughly equally valid options" at the "R^1" position of the A Ring, as Dr. Bannister testified (Bannister 322:16-21, 323:11-25; *see also id.* 317:1-9), that rationale would have applied equally to a number of other options. As Dr. Davies explained, just looking at the '126 patent, there were at least six other "most preferred" substituents at that position, including hydrogen (which appears in 50 out of the 80 examples in the patent). (Davies 561:5-562:5, PDX-243; PTX-36 at Exs. 1-4, 6, 7, 15, and Table 1 (Exs.16-58); PTX-36 at Exs. 13, 14, Table 2.)[43] Dr. Bannister also admitted that, even for this one location, it could also be "chlorine and fluorine and methyl and ethyl and a few others." (Bannister 205:22-23.)

116. **Second Alleged Change:** Even assuming that a POSA would have utilized bioisosterism to change the B Ring phenyl to a thiophene, as Dr. Bannister testified, he ignored

[43] Dr. Bannister was therefore incorrect when he opined that "[i]t's actually the most common example to have an A [R]ing being methyl instead of chloro." (Bannister 204:4-7.)

many other types of bioisosterism. (Davies 575:17-577:4, PDX-253; DTX-208 at 3147.) As Dr. Davies explained, even Dr. Bannister's own Patani reference listed many such potential strategies. (*Id.* (discussing, for example, monovalent atom or group replacements, divalent isostere replacements, trivalent atom or group replacements, and tetrasubstituted atom replacements).) Dr. Bannister did not provided any rationale for choosing a bioisosteric "ring equivalents" strategy (*see* DTX-208 at 3147) over any of these other potential approaches, each of which would have led to numerous compounds other than canagliflozin.

117. Moreover, even if a POSA would have focused on Dr. Bannister's particular bioisosterism strategy, there were various other potential ring structures, including six examples of heteroaryls in various orientations, that were at least equally viable according to Dr. Bannister's own US '315 reference. (*See e.g.*, Davies 568:7-18, PDX-247; PTX-59; DTX-180 (equivalent to US '315) at 63 (including 2- and 3-pyridine (Examples 93 and 94, respectively), 2-oxazole (Examples 95, 99, and 101), 2-thiazole (Examples 96 and 100), 2-benzthiazole (Example 97), and 3-quinoline (Example 98).) And Dr. Bannister did not even address a number of other SGLT prior art references in connection with his analysis. (*See, e.g.*, PTX-65; PTX-68; PTX-67; PTX-61; PTX-64; PTX-89; PTX-70 (references discussed by Dr. Davies, but not Dr. Bannister).)

118. **Third Alleged Change:** In discussing the types of "R4"[44] substituents that could solve the alleged stability problem introduced by his previous phenyl-to-thiophene change, Dr. Bannister expressly admitted that a POSA would have pursued "an alkyl, an aryl, you know, simple things like that." (Bannister 243:17-24, 380:11-14 (agreeing that a POSA would have

[44] Although acknowledging this group could "vary extensively" in the '126 patent, Dr. Bannister sought to dodge this problem by stating that he never attempted to calculate its actual size. (Bannister 368:2-12.)

"consider[ed] using a lower alkyl group from the most preferred genus" of the '126 patent); *see also* Davies 591:7-22.) In fact, that cavalier statement encompasses ***hundreds of thousands*** of potential options, with nothing directing the POSA to select phenyl over all of the other options that Dr. Bannister ignored. (Davies 592:9-593:25, 606:9-19; PTX-36 at 22:46-67, 25:30-26:17.)

119. **Fourth Alleged Change:** Even assuming a POSA would have followed Dr. Bannister's generalized "fluorination" strategy (she would not have), Dr. Bannister acknowledged that a POSA would have tried a "fluorine scan" at "different parts of the molecule" and "everywhere possible," including the A and B Rings. (Bannister 246:18-25, 373:23-375:4; *see also* Davies 601:19-23, 576:2-5, 576:25-577:4.) Dr. Bannister also agreed that a POSA would have had to consider other substituents for the new C Ring apart from fluorine (Bannister 371:14-372:4), as well as move those substituents to different locations (*id.* 372:7-11).

120. Making matters worse, a POSA would not simply have looked at each modification in a vacuum; rather, the permutations for each change needs to be combined with the other changes because a POSA would have had to make all four changes to arrive at canagliflozin. (*See, e.g.*, Davies 617:17-25-618:15, 619:24-621:2, PDX-278 A-D.) As a result, there are countless possible combinations of changes that could have been made applying Dr. Bannister's flawed and hindsight-driven motivations. (COL ¶¶ 230-31.)

(2) Dr. Bannister Ignored Potential Modifications to Other Aspects of the '117 Patent Compound

121. A POSA applying the rationales offered by Dr. Bannister for his alleged motivations would have had considered numerous changes to other aspects of the '117 patent compound, including: (1) modifying the glucose portion; (2) modifying the linker between the glucose and aglycone portions; (3) replacing the phenyl A Ring; (4) modifying ring group

substituents at the locations ignored by Zydus; or (5) modifying the linkers between ring groups. (Davies 601:24-606:19, PDX-267.)

122. *First*, Dr. Davies identified potential substitutions to the glucose portion of the SGLT molecule, including fluorine, which was disclosed to "increase the effect on SGLT" at that particular location. (Davies 602:23-603:6, PDX-268; PTX-70 at [0001], [0010], [0210].) Dr. Bannister himself agreed that "a POSA would consider replacing the oxygen in the glucose moiety with a . . . thio group." (Bannister 375:17-376:5.) These fluorine and thio examples would satisfy Dr. Bannister's criteria of "bioisosteric" changes that "designed around the BMS" patents. (Bannister 376:17-22.)[45]

123. *Second*, apart from carbon and oxygen linkers between the glucose and aglycone portion, Dr. Bannister agreed that the prior art discussed the linker "being [nitrogen]-substituted." (*Id.* 376:23-377:9.) Dr. Bannister further agreed that this was a "bioisosteric change" that would have "designed around the BMS" patents. (*Id.* 377:10-15.)

124. *Third*, Dr. Davies also explained that a POSA following Dr. Bannister's theories could have changed the A Ring phenyl with ring structures like pyrazole or thiophene, as disclosed in WO '737 and US '143. (Davies 603:7-605:8, PDX-269-270; PTX-89 at 7:23-8:3; PTX-64 at [0151], [0167].) Dr. Bannister agreed that any of these modifications would have "escape[d] the claims of the BMS '126 patent," and that there were a "number [of other A Ring possibilities] that could have been tried" based on his own references. (Bannister 379:14-380:5.)

[45] Dr. Bannister asserted that a POSA would not have made these types of glucose modifications because, while companies "patented them, sure," such an SGLT compound was not "ever developed." (Bannister 394:17-395:3.) This hindsight-based opinion directly conflicts with Dr. Bannister's position that a POSA would have utilized a thiophene and third phenyl ring in a C-glucoside, not a single example of which had been previously developed (or even patented). (*See supra* Sections III.C.2-3.)

125. *Fourth*, a POSA would have also considered various substitutions at positions on the phenyl A Ring other than the R^1 position on which Dr. Bannister exclusively focused. (Davies 605:9-24, PDX-271; PTX-59 at 6; *see also* Bannister 381:25-382:10.)

126. *Fifth*, a POSA would have considered using various linkers between the A and B Rings, such as an oxygen, sulfur, and nitrogen. (Davies 605:25-606:13, PDX-272; PTX-36 at 8:1-17; PTX-59 at [0301]-[0302]; *see also* Bannister 380:15-381:24 (agreeing there were "other possibilities," including "a lot of linker alternatives, including [the] placement of the linker and size of the linker").)

127. Just these potential modifications alone—all of which were preferred substitutions in the SGLT prior art—would have added hundreds of thousands of options for a POSA to consider, none of which would have resulted in canagliflozin. (*See, e.g.*, Davies 606:9-19; COL ¶ 231.)

E. Zydus's "Obvious to Try" Analysis Is Incorrect and Ignores Its Own Prior Art

128. Dr. Bannister asserted that his specific proposed modifications to the '117 patent compound would have been "obvious to try." (Bannister 258:14-261:8; Bannister Slide 95.) But this argument shows that Dr. Bannister misunderstands the "obvious to try" analysis, which requires, *inter alia*, that the prior art options be "finite," "small," or "easily traversed." (COL ¶¶ 232-33.) As discussed in Section III.D above, however, there were numerous potential modifications that would have been considered by a POSA, including according to Dr. Bannister's own alleged motivations. (*See, e.g.*, Davies 617:17-618:15, 619:24-621:2, PDX-278 A-D.) This alone is sufficient to reject Dr. Bannister's "obvious to try" assertions.

129. Regardless, Dr. Bannister's "obvious to try" analysis was not representative of the prior art and ignored the teachings of his own prior art references. (Davies 617:3-621:25,

PDX-278 series.) For example, Dr. Bannister offered a Venn diagram that he asserted showed his alleged changes were "obvious to try," which was comprised of three categories: (1) "'117 + '126 patents"; (2) "Easy To Make"; and (3) "Obvious Prior Art." (Bannister Slide 95.) The three categories intersected with an overlap labelled "A few dozen." (*Id.*)

130. Although Dr. Bannister included the "Easy to Make" category, he failed to provide any evidence of what modifications in the other two categories would allegedly have not been easy for a POSA to make.[46] (Davies 594:18-21.) The undisputed evidence at trial showed that a POSA would not have had any difficulty making any of the various options ignored by Dr. Bannister. (*Id.* 594:22-595:5, 617:3-15, PDX-278.) Dr. Davies also explained the numerous other flaws with Dr. Bannister's "obvious to try" analysis (Davies 618:18-23, PDX-278E; *id.* 618:24-619:4, PDX-278F; *id.* 619:6-11, 621:19-22, PDX-278G; *id.* 619:12-19, 621:23-25, PDX-278H), which should be rejected. (COL ¶¶ 232-33, 235.)

F. Zydus Did Not Prove That a POSA Would Have Had a Reasonable Expectation of Success

131. Even assuming, *arguendo*, that a POSA would have been motivated by the prior art to modify the '117 patent compound in the manner Zydus claims, Zydus did not prove by clear and convincing evidence that a POSA would have had a reasonable expectation of success that these modifications would yield an improved antidiabetic compound in light of the complexities of antidiabetic drug design and unpredictability of medicinal chemistry. (COL ¶ 234.)

[46] Regardless, Zydus did not prove that a POSA would have been motivated to make changes based on ease of synthesis, especially when the goal of a POSA was to make an improved antidiabetic agent. (Davies 594:1-595:5; *see also supra* Section III.A.)

132. Dr. Bannister alleged that a POSA would have understood that an SGLT inhibitor must: (1) selectively inhibit SGLT; (2) induce urinary glucose excretion when administered orally; (3) lower blood glucose when administered orally; (4) result in an aglycone (produced by hydrolysis) that does not inhibit GLUT; and (5) have low kidney toxicity. (Bannister 385:16-386:22; *see also* Davies 607:1-14, PDX-273.) Dr. Bannister did not establish, however, that a POSA would have reasonably expected his proposed modifications to successfully produce a compound having these five properties.

133. Dr. Bannister's arguments failed from the outset when he admitted that the prior art lacked any biological data for the '117 patent compound, including a complete absence of any evidence of efficacy via oral administration or lack of toxicity. (*See supra* Section III.B.2.) Without this information, a POSA would not have had any reasonable expectation of these properties in the resultant compound after making the four changes proposed by Dr. Bannister. (Davies 607:17-608:22, PDX-274.)

134. Making matters worse for Zydus, Dr. Bannister admitted that he provided (1) no prior art examples of an SGLT inhibitor with a 2,5 di-substituted thiophene at the B Ring, (2) no prior art examples of a C-glucoside containing a thiophene ring at any location, and (3) no example in the prior art of a compound with a phenyl A Ring, thiophene B Ring, and another distal phenyl ring. (Davies 607:1-608:22, PDX-274; Bannister 388:22-389:3, 389:11-19.) Accordingly, a POSA would not have had any expectation regarding the impact that each of these changes would have had on the relevant properties of the resultant molecule. (*Id.*)

135. Moreover, Dr. Bannister's own references taught that his proposed changes were undesirable. For example, methyl and thiophene were known in the prior art to have potential detrimental effects on stability and toxicity, respectively. (*See, e.g.*, Davies 612:12-18,

PDX-277; *see supra* Sections III.C.1.b, III.C.3.b.) The thiophene group was also taught to be incompatible with C-glucosides in the '126 patent, and a third phenyl ring fell outside of that patent's most preferred genus. (*See, e.g.*, Davies 612:12-20, PDX-277; *see supra* Section III.C.2.a.) By ignoring the preferred teachings of his own references, Dr. Bannister further dispelled any reasonable expectation of success for his proposed modifications.

136. Further, Dr. Davies provided various examples of the unpredictability of drug discovery relating to SGLT-inhibiting compounds, including single alleged "bioisosteric replacements" that result in significant activity changes. (Davies 608:23-609:23, PDX-275; PTX-108 at 25-26; *see also* Davies 609:24-611:2, PDX-276; PTX-122 at 5314 (Table 1).)

137. The lack of a reasonable expectation of success is amplified because Dr. Bannister's analysis requires a POSA to have made ***multiple modifications***, one after another, without knowledge of the effects of any one of them. (Davies 608:1-22, PDX-274.) For example, as Dr. Bannister admitted, the prior art did not support "multiple bioisosteric modifications"—*i.e.*, the foundation of his obviousness analysis (Bannister 340:13-25 (contending that three bioisosteric changes would have been made by a POSA))—"being made at the same time to a given compound" (Bannister 341:8-12; *see also id.* 341:14-17).

138. In fact, even if Zydus proved that a POSA would have had a reasonable expectation of success for any of its alleged bioisosteric changes, Dr. Bannister admitted that changing an ethoxy to a phenyl ring was ***not*** recognized as a bioisosteric modification in the prior art. (*Id.* 340:2-341:1.) Since his basis for reasonable expectation of success hinged solely on "bioisosterism" (*see, e.g., id.* 180:24-181:25), Dr. Bannister did not provide any evidence to prove that a POSA would have had a reasonable expectation of success when changing the 4-ethoxy to a phenyl ring (Davies 608:6-16, PDX-274).

139. In sum, Zydus has failed to prove by clear and convincing evidence that a POSA would have had a reasonable expectation of success that Dr. Bannister's proposed modifications would have yielded an improved antidiabetic compound in light of the complexities of antidiabetic drug design and the prior art. (COL ¶¶ 234, 235.)

IV. Zydus Did Not Prove that Claim 22 of the '219 Patent or Claim 26 of the '403 Patent Would Have Been Obvious

140. Apart from a conclusory, unsupported summary statement that claim 22 of the '219 patent and claim 26 of the '403 patent would have been obvious (Bannister 110:7-11), Dr. Bannister did not provide any testimony, or identify any prior art, to support Zydus's invalidity theories with respect to these specific claims.[47] This is insufficient on its face to meet Zydus's burden to prove obviousness by clear and convincing evidence. (COL ¶ 236.)

141. Dr. Davies testified that claim 22 of the '219 patent (directed to a method of treating or delaying the progression of type 2 diabetes using canagliflozin) and claim 26 of the '403 patent (directed to a combination composition containing canagliflozin and another antidiabetic agent, metformin) contain additional requirements, which Zydus has not established were taught by the prior art. (Davies 505:10-23, 611:3-21, PDX-202; PTX-1 at 223:5-7, 224:40-56; PTX-2 at 220:45-46; PTX-3 at 221:26-27.)

142. Zydus therefore failed to carry its burden of proving, by clear and convincing evidence, invalidity of claims 12 and 20 of the '788 patent, claim 22 of the '219 patent, and claim 26 of the '403 patent. (COL ¶ 236.)

[47] Dr. Bannister's limited discussion of the '219 patent focused on his (cursory) obviousness-type double patenting analysis, which did not address asserted claim 22. (Bannister 264:13-266:4, Bannister Slides 101-102.)

V. Objective Indicia of Nonobviousness Confirm That Zydus Did Not Establish Obviousness of the Asserted Claims by Clear and Convincing Evidence

143. Objective indicia provide tangible evidence of the economic and motivational issues relevant to the nonobviousness of an invention. (COL ¶¶ 237-38.) Zydus carries the burden of establishing obviousness of the asserted claims without the use of hindsight and by taking into account relevant objective indicia of nonobviousness. (*Id.*) Here, a nexus between the claimed invention and the evidence of objective indicia is presumed because all of the asserted claims cover canagliflozin, the active ingredient in Invokana® and Invokamet®, which provides the clinical benefits described below. (*See, e.g.*, Davies 505:24-506:13, PDX-203; Gavin 743:10-19, PDX-306; Bannister 161:18-21; Williams 1038:3-17.) Despite challenging this issue throughout this case, Zydus's witnesses did not provide any evidence to rebut this presumption. (COL ¶ 239.)

A. Canagliflozin Has Unexpected Clinical Benefits

(1) Canagliflozin Has Demonstrated Superior Glycemic Control in Diabetic Patients Compared to Dapagliflozin

144. Canagliflozin has demonstrated superior glycemic control when compared to the '117 patent compound, Zydus's alleged closest prior art compound, as demonstrated by scientific analyses and FDA-approved labeling.

145. As Dr. Gavin explained, canagliflozin's superior glycemic control, evidenced by reduced blood glucose levels upon oral administration, has been demonstrated through various statistical tools that provide valuable scientific evidence, including meta-analyses and retrospective cohort studies.[48] (Gavin 750:6-765:1, PDX-307.) A reduction in blood glucose

[48] Dr. Williams acknowledged that these statistical tools are accepted in the scientific community. (Williams 1117:1-12.)

levels helps type 2 diabetes patients achieve treatment goals, and is associated with limiting complications caused by high blood glucose levels. (Gavin 731:25-732:8, 735:14-736:3.) Even a small numerical reduction in A1C can be extremely meaningful to a patient's outcome over a prolonged period of time, since type 2 diabetes is a chronic, progressive disease that can result in the failure of many biological systems over time. (Gavin 735:22-736:3; *see supra* Section II.B.)

146. Dr. Gavin discussed the peer-reviewed Zaccardi meta-analysis,[49] which analyzed data from 38 randomized controlled clinical trials involving more than 23,000 participants, "to assess the comparative efficacy and safety of [SGLT2] inhibitors in adults with type 2 diabetes." (PTX-238 at 783; *see also* Gavin 763:7-764:17.) The data showed that the highest FDA-approved dose of canagliflozin reduced A1C and fasting plasma glucose levels to a statistically significant greater extent than the highest FDA-approved dose of dapagliflozin.[50] (*See, e.g.*, Gavin 763:7-764:17, 806:25-807:8; PTX-238 at 783, 791; *see also* Williams 1118:2-17, 1118:23-1119:1.) Based on these results, the authors concluded that "SGLT2 inhibitors are effective in improving cardiometabolic markers in type 2 diabetes, with canagliflozin 300 mg performing better in this respect than other inhibitors." (PTX-238 at 783; *see also* Gavin 763:3-764:17.)

[49] Meta-analyses can compare large amounts of data from multiple clinical trials to determine the comparative effectiveness of pharmaceutical treatments, and have been recognized for their value in informing clinical practice. (Gavin 761:1-7, 763:7-25, 806:25-807:8; PTX-238.)

[50] When analyzing comparative efficacy of FDA-approved drugs with multiple doses, to provide an apples-to apples comparison, clinical studies compare the highest-approved doses of each drug (*e.g.*, 300 mg canagliflozin and 10 mg dapagliflozin) because these doses have been demonstrated to provide the maximum clinical effect. (Gavin 754:22-757:9.)

147. Dr. Gavin also explained that Blonde, a retrospective, real-world cohort study,[51] analyzed data from type 2 diabetes patients taking either dapagliflozin or canagliflozin at their highest FDA-approved dosages. (Gavin 761:9-762:24; PTX-182 at 1-2, 9.) The study concluded that patients taking canagliflozin had larger A1C reduction after six months and better A1C goal attainment. (Gavin 762:9-24; PTX-182 at 1-2, 9.) The patients in the study receiving 300 mg of canagliflozin were also less likely to discontinue their treatment than those on 10 mg of dapagliflozin, which is critical for disease management. (Gavin 762:20-24; PTX-182 at 1-2, 8.)

148. Consistent with the above studies showing the greater efficacy of canagliflozin, Sha, a head-to-head Phase I study in healthy participants comparing canagliflozin to dapagliflozin, also demonstrated greater lowering of renal threshold for glucose excretion,[52] as well as a greater increase in urinary glucose excretion, for canagliflozin. (Gavin 751:7-754:18; PTX-231 at 188, 191-96; *see also* Bannister 1103:6-9.) This head-to-head study also determined that canagliflozin provided the additive benefit of delayed and reduced postprandial glucose excursion (*i.e.*, the change in blood glucose levels after a meal is consumed), while dapagliflozin did not.[53] (Gavin 752:7-15, 753:1-20, 757:10-25; PTX-231 at 188, 191-96.) These results are significant because glucose levels are typically at their peak after a meal is ingested, and thus a drug that provides this type of glucose-lowering action helps to lower blood glucose when at its highest levels. (Gavin 753:1-20.)

---

[51] Cohort studies review the long-term evaluations of patients using a pharmaceutical treatment as part of their normal treatment regimen and have been recognized for their value in informing clinical practice. (Gavin 761:12-762:15.)

[52] This refers to the maximum amount of glucose in the kidneys that can be reabsorbed into the bloodstream. (Gavin 753:21-754:18.) Lowering the renal threshold allows glucose to be excreted in the urine sooner than normally expected, causing lower blood glucose levels. (*Id.*)

[53] One possible reason for this difference is canagliflozin's ability to inhibit SGLT1, which reduces glucose uptake in the gut after a person eats. (Gavin 757:14-25; PTX-231 at 188, 195.)

149. As canagliflozin was the first FDA-approved SGLT2 inhibitor, dapagliflozin could not be used as the direct head-to-head comparator to demonstrate canagliflozin's efficacy in a Phase III clinical trial. (Gavin 750:18-751:6.) Instead, canagliflozin was compared to other antidiabetic drugs approved at the time, including sitaglipton, a DPP-4 inhibitor. (Gavin 758:11-25; PTX-1086 at 11.) The results of this head-to-head study demonstrated that canagliflozin was statistically superior in lowering A1C levels in type 2 diabetes patients. (Gavin 760:5-10; PTX-1086 at 11.) In contrast, when dapagliflozin was compared in a similar head-to-head study against the same sitaglipton drug, it did not demonstrate the same statistical superiority as canagliflozin. (Gavin 760:11-16; *see also* Williams 1114:9-1116:20, PTX-2000.) This provides further, indirect evidence of the clinical benefits of canagliflozin compared to dapagliflozin.

150. Dr. Williams did not dispute the accuracy of any of the peer-reviewed data discussed by Dr. Gavin, but instead argued that this unexpected property can be proven only through large, randomized Phase III head-to-head clinical studies. (Williams 1060:9-23, 1103:16-23.) This argument, however, conflates FDA marketing standards[54] with the standard applied for determining unexpected properties, where the Federal Circuit has explicitly permitted indirect showings of unexpected superiority. (COL ¶ 240.)

151. Dr. Williams also attempted to respond to Dr. Gavin's opinion by presenting his personal preference for prescribing Jardiance® (empagliflozin) instead of Invokana® (canagliflozin). (*See, e.g.*, Williams 1073:4-6.) Because empagliflozin, however, was not known in the prior art, Dr. William's opinion regarding Jardiance® is legally irrelevant to

[54] Dr. Gavin also explained that the FDA has begun to recognize the value of real-world evidence, such as from cohort studies and meta-analyses. (Gavin 797:3-10, 806:23-807:8.)

unexpected properties. (COL ¶ 240.) Notably, Dr. Williams never testified that he preferred Farxiga® (dapagliflozin) over Invokana® (canagliflozin), or considered Farxiga® to be superior to Invokana®.

(2) The Clinical Benefits of Canagliflozin Compared to Dapagliflozin Would Have Been Unexpected to a POSA

152. Dr. Bannister asserted that a POSA would have been motivated to develop a "me too" SGLT2 inhibitor, *i.e.*, a compound that did not perform "any better" than the '117 patent compound, but fell outside the scope of BMS's C-glucoside patents. (Bannister 175:2-176:6.) Nor did Dr. Bannister assert that any of the four changes being made to the '117 patent compound would be expected to result in an improved compound. As shown above in Section V.A.1, however, canagliflozin actually provides superior clinical outcomes for type 2 diabetes patients.

153. Furthermore, Zydus shifted (once again) its position at trial to argue that MTPC's internal confidential documents, which are not publicly available, somehow demonstrated a lack of unexpected results.[55] (*See infra* Section V.F.) In contrast to Dr. Gavin's evaluation of clinical outcomes, Dr. Bannister focused exclusively on MTPC's *in vitro* and *in vivo* preclinical animal testing data to assert a lack of unexpected results. (*See, e.g.*, Bannister 247:21-248:7, 262:10-263:19, 263:20-264:8, Bannister Slides 98-99; DTX-90.) If anything, these data further support Dr. Gavin's testimony regarding the unexpected benefits of canagliflozin compared to dapagliflozin with respect to clinical outcomes. Specifically, Dr. Bannister's own conclusion that canagliflozin was not "as promising as" dapagliflozin based on this ***preclinical*** data (Bannister 263:8-19) further confirms the unexpected nature of these superior clinical outcomes.

[55] As discussed in Section V.F below, Dr. Bannister's testimony regarding MTPC's internal efforts contained various inaccuracies concerning the inventors' efforts.

154. For example, Dr. Bannister asserted that SGLT1 inhibition is "something you don't want to do," and that a compound would need "to be selective [with respect to] SGTL2 versus SGLT1." (*See, e.g.*, Bannister 121:12-122:23, Bannister Slide 12; *see also* Bannister 385:20-25.) As Dr. Davies explained, however, MTPC's internal testing data showed that canagliflozin is less selective for SGLT2 versus SGLT1 compared to dapagliflozin, which (under Dr. Bannister's analysis) would have led a POSA to believe that dapagliflozin would be more effective. (Davies 613:10-614:9.) That canagliflozin actually provides patients with meaningfully improved clinical outcomes when compared to dapagliflozin would therefore have been unexpected in 2003. (COL ¶ 240.)

B. Skepticism Surrounded the Development of SGLT Inhibitors as a Type 2 Diabetes Treatment

155. Until long after the invention of canagliflozin (*see* Section III.B), clinicians and researchers in the diabetes field were skeptical of the use of SGLT inhibitors as a potential type 2 diabetes treatment and, instead, focused on other drug categories. (Gavin 743:5-9; Davies 531:19-25; COL ¶ 241.) As Dr. Gavin explained, throughout his career, increased sugar in the urine was seen as an unequivocal marker of the disease, and something to be avoided. (Gavin 740:8-741:12, PDX-305.) Researchers and clinicians in the type 2 diabetes field remarked that the idea of purposefully increasing sugar output in the urine to control glucose levels was counterintuitive to the historical thinking about diabetes pathophysiology, and initially appeared to be a strategy that might worsen the damaging effects of the disease, including to the kidneys. (Gavin 740:8-743:4, 779:3-14, 788:16-789:3, PDX-305; PTX-186 at 4, PTX-188 at 1-2.) For example, flooding the kidneys with excess glucose raised infection- and renal damage-related concerns. (Gavin 741:16-24.)

156. Further evidence of this skepticism was demonstrated by review articles from 2000-2003 documenting viable type 2 diabetes treatment targets, which did not mention SGLT inhibitors among the numerous promising examples. (Davies 532:1-21; 534:4-12, PDX-223; *see also* Bannister 286:11-15; Williams 1078:11-1079:21; COL ¶ 241.) For example, Dr. Williams agreed that, in a 2003 review article discussing various therapeutic strategies for antidiabetic agents, SGLT2 inhibitors were not among the list of approximately 15 classes of compounds involved in active research.[56] (Williams 1078:11-1079:21; PTX-113 at 170.) Apart from MTPC's efforts with T-1095, Dr. Williams did not provide any prior art to rebut the evidence of skepticism about which Drs. Gavin and Davies testified. (Williams 1101:11-1102:5.)

157. Despite this initial skepticism, MTPC researchers dedicated significant time and resources to the discovery and development of canagliflozin, and the Invokana® Products eventually emerged as important and novel treatment options for type 2 diabetes patients. (*See supra* Sections II.B, V.A-B.) For example, the Invokana® Products were shown to provide a renal protective benefit, exemplified by the FDA approved renal indication in 2019, which was the first of its kind for an SGLT compound. (Gavin 743:12-19; 746:22-23, 804:12-17, PDX-306; Sims 948:6-7.)

C. Failure of Others to Develop a SGLT Inhibitor

158. As Dr. Bannister had to recognize, researchers studying the SGLT pathway attempted to design and develop inhibitors as potential antidiabetic agents, but encountered many

[56] Dr. Williams admitted that he did not have any involvement in research relating to antidiabetic agents between January 2001 and April 2004 (Williams 1098:22-1099:4), and did not consult with any pharmaceutical companies with respect to research relating to antidiabetic agents between 2001 and 2004 (*id.* 1099:5-1100:12). Moreover, despite asserting that he was aware of research relating to SGLT compounds before 2004, Dr. Williams could not identify a single SGLT compound being researched, or company conducting SGLT research, that he was aware of during the relevant time period (apart from T-1095). (*Id.* 1101:1-4, 1101:16-1102:5.)

failures and dead ends. (Bannister 249:10-19.) In fact, according to Dr. Bannister, there were "a significant number[] of companies that did not achieve the goal of introducing a useful SGLT inhibitor." (*Id.* 287:5-8.)

159. For example, MTPC scientists reported on their development of T-1095/T-1095A, but MTPC eventually ceased its development due to internal, confidential study results. (*See infra* Section V.F; Bannister 249:10-19.) Additional SGLT inhibitors, such as sergliflozin, were being developed in the mid-2000s, but never reached the U.S. market. (*See* Williams 1048:2-4 (listing the SGLT2 inhibitors available on the U.S. market), 1081:11-1085:10, 1088:23-1089:19 (explaining the development of sergliflozin continued into the mid-2000s); DTX-151 at 1146; *see also* Davies 546:4-547:7, PDX-234 (providing additional candidates from the mid-2000s, none of which made it to the U.S. market).) Where these others failed, MTPC was able to succeed with the discovery and development of canagliflozin and eventual approval of Invokana® as the first FDA-approved SGLT inhibitor. (COL ¶ 242.)

D. Copying and Acquiescence by Potential Generic Competitors

160. To date, at least 14 pharmaceutical companies are seeking to market generic versions of the Invokana® Products and have challenged Orange Book-listed patents covering these drugs. (*See e.g.*, Civil Action No. 17-5005, D.I. 1, 158, 195, 207, 276 (D.N.J 2017).) Of those 14 generic companies, only one—Zydus—is challenging the validity of the asserted claims of the patents-in-suit as obvious. (*See* Plaintiffs' Opening 87:13-88:12, PDX-58.)[57] Many of these companies are currently challenging other patents covering the Invokana® Products

[57] Before agreeing to the validity of the asserted claims, the four other defendant generic companies that were previously part of this litigation agreed to withdraw similar obviousness arguments shortly after receiving Plaintiffs' responses to their Invalidity Contentions. (SF ¶ 21 n.5.) One of the defendants even withdrew its challenge of the '788 patent completely by converting its ANDA to include a Paragraph III certification. (D.I. 129; *see also supra* n.1.)

(*e.g.*, Civil Action No. 17-5005, J. Bumb), but have respected the validity of the asserted claims in this case. That numerous other generic companies have acknowledged the validity of the asserted claims further confirms their nonobviousness. (COL ¶ 243.)

E. Commercial Success

[redacted]

[58] Mr. Sims is an economist at Charles River Associates, an international business consulting firm, with more than 35 years of experience consulting on matters involving financial analysis, including for the pharmaceutical industry. (Sims 932:25-935:23; PTX-26.) Mr. Sims earned a Bachelor of Commerce degree from the University of Calgary in 1976 and an MBA degree from Northwestern University J.L. Kellogg Graduate School in 1980. (*Id.*)

[59] Three SGLT inhibitors have entered the U.S. market since Invokana®'s launch. (Sims 943:24-944:24, 963:9-964:5, PDX-504; PTX-233; PTX-305; PTX-311; McDuff 449:18-25, 450:18-20.) In addition, although it was recently removed in August 2020, a "black box warning" was placed on Invokana®'s label in 2017. (*See e.g.*, Gavin 748:20-23, 749:3-7; Sims 945:12-15, 947:10-23, 948:8-10, 948:19-949:6, PDX-504; PTX-249 at 4.)

[redacted]

[redacted]

[redacted]

[redacted]

F. MTPC's Internal, Non-Prior Art Work Does Not Support Zydus's Obviousness Defense

175. Before trial, Zydus sought to use the inventors' own work as part of its obviousness defense. (*See, e.g.*, D.I. 170 ¶¶ 575, 643, 714, 735, 767.) Of course, this implicates impermissible hindsight and is not an appropriate basis for asserting obviousness, which depends on what a POSA would have believed at the time of the invention based on the prior art.[63] At trial, Zydus once again shifted its position to argue that it was not using the inventors' own work "to prove obviousness," but rather to somehow show "that there were no unexpected results." (Zydus's Counsel 250:17-23; *see also* Bannister Slides 98-99.) In light of Zydus's representations, there is no dispute that Zydus has disclaimed any attempted use of MTPC's

[63] The patent statute makes clear that "[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103; *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."); *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000) (finding that "using the inventors' success as evidence that the success would have been expected" was impermissible hindsight). Dr. Bannister admitted (after being impeached), however, that he considered elements of MTPC's internal documents "before forming [his] opinions in this case." (Bannister 383:5-384:4.)

internal documents, or Dr. Kawanishi's testimony regarding the invention,[64] to support Zydus's lead compound, motivation to modify, or reasonable expectation of success assertions.

176. With regard to Zydus's assertion of "no unexpected results,"[65] the evidence at trial showed that Zydus had mischaracterized the inventors' work. As discussed above, the evidence at trial demonstrated that canagliflozin showed unexpected results (*see supra* Section V.A), which, to the extent relevant, the inventors' work only further confirms.

177. The inventors' discovery of canagliflozin was not the result of a process predicated by expectations regarding what would or would not result in a viable SGLT inhibitor. Far from it, MTPC's work involved the persistent, confidential (*i.e.*, non-prior art) work of more than 13 scientists and their supporting technicians, who performed thousands of experiments from the start of the project through the discovery of canagliflozin in 2003.[66] (Kawanishi 825:7-827:24, 861:16-23, PDX-402; *see also* Nomura Tr. 115:10-18 ("Little by little by little ideas were accumulated and eventually the final product came to be. So it was a gradual accumulation of a lot of ideas.").) If the results of this project were expected, as Zydus incorrectly argues, then

---

[64] Dr. Kawanishi was asked to testify at trial because, before trial, Zydus (without any basis) disputed the invention date. At trial, Zydus's counsel did not question Dr. Kawanishi's support for the October 29, 2003 invention date, so it is undisputed. (*See supra* Section III.A.) This reflects yet another shift in position by Zydus.

[65] Unexpected results, when shown, may rebut an inference of obviousness. The absence of a showing of unexpected results, however, does ***not*** constitute evidence of obviousness. (COL ¶ 237.)

[66] Zydus's counsel brazenly claimed that canagliflozin was "a rip-off" of another pharmaceutical company's work. (Zydus's Opening 40:7-9.) If anything, this baseless allegation simply reveals yet another of Zydus's frivolous positions. For example, Zydus did not provide any evidence that any other entity conceived canagliflozin, whether before, during, or after the time when MTPC discovered this new molecule after extensive experimental work. In truth, Zydus is the only entity seeking to appropriate MTPC's invention, with its hindsight-based claim—concocted solely by lawyers for litigation—that this innovative drug was somehow obvious to a POSA.

MTPC's scientists would not have needed to perform the significant experimental work discussed at trial.

178. MTPC's SGLT project instead illustrates the endless possibilities, unpredictability, and complexity associated with attempting to develop an improved SGLT inhibitor during the relevant time period. Although the inventor's expectations are irrelevant as a matter of law (*see supra* ¶ 175 n.63), the evidence demonstrates that the inventors needed to try a vast number of different groups at a variety of locations based on their experience, intuition, and internal data—groups and locations that Zydus's oversimplified and hindsight-based approach ignores, as discussed above—to arrive at a successful SGLT inhibitor.[67] (*See, e.g.*, Kawanishi 839:8-841:1, PDX-403.)

179. For example, Dr. Bannister asserted that a POSA would have expected that O-glucosides would be metabolically unstable and could not serve as viable SGLT inhibitors. (*See supra* Section III.B.3.) As Dr. Kawanishi explained, however, MTPC continued its efforts to identify an O-glucoside-type SGLT inhibitor even after BMS's C-glucosides were disclosed.[68] (Kawanishi 828:18-21, 833:4-20, PTX-501 at 90; *see also* PDX-402.)

180. Dr. Kawanishi also provided examples of numerous different modifications with which MTPC scientists confidentially experimented between 2002 and 2004, including:

---

[67] Dr. Bannister admitted that he did not conduct a complete analysis of MTPC's SGLT research documents, and did not fully review the MTPC documents he referenced during his testimony. (Bannister 384:5-13.) Instead, he reviewed only the document portions provided by Zydus's counsel. (*Id.* 384:23-25.) Dr. Bannister also agreed that he had no independent knowledge regarding MTPC's internal SGLT work. (*Id.* 384:20-22.)

[68] In fact, MTPC continued these efforts even after the "poor" clinical trials results for MTPC's O-glucoside clinical candidate (T-1095), which were highly confidential and not available in the prior art. (Kawanishi 825:9-24.)

- various different substitutions of the glucose portion (Kawanishi 843:9-844:12, PDX-404 (submitted as a summary of MTPC's voluminous laboratory notebooks, including PTX-517 at 4, PTX-518 at 36, PTX-578 at 120, and PTX-765 at 130));

- various different atoms in the linker between the glucose and aglycone portions (Kawanishi 844:19-845:11, PDX-405 (submitted as a summary of MTPC's voluminous laboratory notebooks, including PTX-498 at 150, PTX-527 at 36, PTX-543 at 48, PTX-566 at 18, and PTX-547 at 144));

- a variety of different aryl and non-aryl groups at the A Ring location (Kawanishi 846:19-847:12, 849:6-15, PDX-406 (submitted as a summary of MTPC's voluminous laboratory notebooks, including PTX-536 at 58, PTX-538 at 104, PTX-552 at 54, PTX-548 at 168, PTX-557 at 180, and PTX-572 at 172)); and

- a variety of different aryl and non-aryl groups at the B Ring location (Kawanishi 848:6-23, 849:16-24, PDX-407 (submitted as a summary of MTPC's voluminous laboratory notebooks, including PTX-541 at 176, PTX-491 at 174, PTX-594 at 12, PTX-557 at 176, PTX-595 at 40, and PTX-660 at 12)).

181. Moreover, MTPC found that, out of the 127 novel MTPC compounds tested, only 27 (~20%) demonstrated strong inhibitory activity. (Bannister Slide 93, DTX-88.) And out of the 27 "patent" compounds that MTPC evaluated, only seven (~25%) demonstrated strong inhibitory activity. (*Id.*)[69] This is entirely consistent with the prior art evidence Dr. Davies utilized to illustrate the unpredictability in the SGLT field that a POSA would have faced, and also undermines Dr. Bannister's overreliance on a patent's described activity without supporting pharmacological data. (*See supra* Sections III.B.2, III.F.)

182. Ignoring the vast majority of MTPC's efforts, Zydus focused exclusively on a small subset of that work pertaining to certain BMS compounds in a misguided attempt to rebut

[69] Despite Dr. Bannister's attempt to portray DTX-88 as relevant to unexpected results (*see, e.g.*, Bannister Slides 92-93), it was created in 2005—almost two years ***after*** the inventors synthesized canagliflozin. Zydus failed to establish how such a post-2003 summary of extensive preclinical research by a team of highly skilled scientists could disprove canagliflozin's unexpected clinical superiority. (COL ¶ 240.)

canagliflozin's unexpected properties.[70] As Dr. Kawanishi explained, other companies' compounds from the literature served only as "reference compounds" to benchmark the progress of MTPC's own work.[71] (Kawanishi 837:19-839:7; *see also id*. 903:1-4, 904:15-17, 906:23-907:9 (explaining that DTX-85 was written "quite a while after the discovery of canagliflozin" and was "geared toward [an] audience" that was not "sophisticated in chemistry," and that "[t]he work of using a heteroaromatic ring and modifying compounds was not something that was done in a short period of time"); Nomura Tr. 227:21-230:15 (testifying that a BMS patent compound was not "the starting point of the research that . . . led ultimately to canagliflozin").)

183. Dr. Bannister also focused on a single set of MTPC experiments (DTX-120), which he mischaracterized as a "plan on whether this idea of a phenyl-to-thiophene swap is a good one." (Bannister 260:17-18.) As Dr. Kawanishi explained, he personally created DTX-120, which reflected his effort to make "a plan to introduce to the aglycone portion of the molecule, a ring in addition to the A ring and B ring." (Kawanishi 853:2-9.) In other words, Dr. Kawanishi created DTX-120 to determine the benefit of his idea to add a third aryl ring—which, again, would have been unnecessary if this idea was expected to work in the first place. This has nothing to do with Dr. Bannister's self-contradictory and unsupported assertions of bioisosterism.

---

[70] The BMS compound that Zydus focused on, however, was Example 1 of the '126 patent—***not*** the '117 patent compound. (*See, e.g.*, Bannister Slides 86-87; Kawanishi 894:1-2.)

[71] Although MTPC chemists made and tested the '117 patent compound, it occurred ***nine months*** after they began making and testing many other compounds from the literature, including from pharmaceutical companies besides BMS. (Kawanishi 834:1-12, 835:12-836:9, 837:6-18, PDX-402.) Despite Dr. Bannister's testimony to the contrary, the '117 patent disclosure was made publicly available on September 26, 2002. (*See* DTX-87 at 1 ("Prior Publication Data").)

184. Moreover, the extra-ordinarily skilled Dr. Kawanishi testified that, when he told his fellow MTPC chemists about his idea for a third aryl ring, they thought that SGLT activity would "most likely not be maintained, that it wouldn't work" (*Id.* 856:19-25). Because "[t]he medicinal chemist members on the SGLT project were negative towards" Dr. Kawanishi's idea for a third aryl ring, he "wasn't given the researchers for implementing this synthesis plan of mine of 40 compounds." (*Id.* 857:24-858:2.)

185. It was only because of Dr. Kawanishi's "strong personal conviction" that he pressed the matter further and "asked for reinforcement, for more people, researchers, to implement this plan." (*Id*. 857:17-858:5.) And it was this work that ultimately led to the discovery of canagliflozin, which has been used to treat millions of patients suffering from type 2 diabetes, and for which Dr. Kawanishi and his colleagues have "received multiple awards." (*Id*. 862:8-863:14.) Thus, to the extent Zydus's attempted reliance on MTPC's internal work has any relevance to canagliflozin's unexpected clinical results (it does not), it only further confirms the nonobviousness of the asserted claims.

VI. Zydus Did Not Prove Obviousness-Type Double Patenting by Clear and Convincing Evidence

A. The Later-Filed '219 Patent Does Not Constitute a Proper Basis for Invalidating the '788 Patent's Statutorily Authorized PTA

186. Zydus's allegation that the '788 patent's PTA can serve as a basis for obviousness-type double patenting over the '219 patent is incorrect as a matter of Federal Circuit law. (COL Section VII.D.1.)

187. The application that led to the '788 patent was filed on January 31, 2005, claimed priority to an application filed on July 30, 2004, and issued as the '788 patent on May 17, 2011. (PTX-1.0002; PDX-712; PDX-604.) Although the '788 patent would have expired on July 30, 2024 (corresponding to a roughly 13-year patent term), the PTO granted a PTA of 1,079 days

under 35 U.S.C. § 154(b) based upon delays caused by the PTO during prosecution. (*Id.*) As such, a statutorily authorized extension of the '788 patent term was granted, resulting in an approximately 16-year period during which the '788 patent could be enforced. (*Id.*) This is precisely what Congress had in mind in 1995, when it changed the way patent terms are calculated while providing for "Patent Term Guarantees" under 35 U.S.C. § 154(b). (COL ¶ 245; *see also* PDX-603 (discussed at Plaintiffs' Opening 1169:6-1170:6).)

188. The application that led to the '219 patent was filed on July 1, 2011, claimed priority to the same application as the '788 patent, and issued as the '219 patent on July 17, 2012. (PTX-2.0002; PDX-712, PDX-604.) The '219 patent had a shorter prosecution, however, which led to it issuing without the need to adjust the patent term. (*Id.*) Because the '219 patent claimed priority to the same July 30, 2004 application as the '788 patent, the '219 patent also had the same expiration as the '788 patent before the latter was extended by the PTA (*i.e.*, July 30, 2024)—resulting in a roughly 12-year patent term.[72] (PDX-712; PDX-604.)

189. Contrary to Zydus's claims, there is nothing improper about the longer term of the original '788 patent. In fact, this is simply an instance where a subsequent patent in a patent family received a shorter term than the earlier-filed and earlier-issued patent—*i.e.*, the exact opposite of what obviousness-type double patenting is intended to prevent—because the conditions for a statutorily authorized PTA were met for only one of the patents. (COL ¶ 249.)

190. Because the '788 and '219 patents would both expire at the same time but for the "Patent Term Guarantee[]" resulting from the PTO's delay, there is no "gamesmanship" here. (COL ¶ 248.) Nor has Zydus ever alleged any "gamesmanship," including at trial. (*See, e.g.*,

[72] The '219 patent also has a PTE under 35 U.S.C, § 156 that will not expire until April 11, 2025. (PTX-5.0698.) Zydus did not allege obviousness-type double patenting based on this PTE.

Zydus's Opening 1154:19-1168:4.) Moreover, as a matter of Federal Circuit (and Supreme Court) law, the judicially created doctrine of obviousness-type double patenting should not be used to cut short the '788 patent's statutorily authorized PTA. (COL ¶¶ 246-47.)

B. The '788 Patent Claims Are Protected under the 35 U.S.C. § 121 Safe Harbor

191. Even if Zydus could establish that the '219 patent could properly serve as an obviousness-type double patenting reference, the '219 patent claims cannot invalidate claims 12 and 20 of the '788 patent because of the statutory safe harbor set forth in 35 U.S.C. § 121, which provides an independent basis for rejecting Zydus's defense. (COL Section VII.D.2.)

(1) The '219 Patent Was Filed as a Divisional Application "as a Result of" the Examiners' Restriction Requirement

192. There is no dispute that: (1) the Examiners imposed a restriction that required the separation of, *inter alia*, the compound and method-of-treatment claims; (2) this restriction requirement remained in place, including with respect to the method-of-treatment claims;[73] and (3) the divisional '219 patent claims cover the restricted subject matter. Under the plain language of 35 U.S.C. § 121 and Federal Circuit case law, the safe harbor inquiry ends here.[74] (COL ¶¶ 251-52.)

---

[73] One of Zydus's two arguments in its Invalidity Contentions for why the Section 121 safe harbor does not apply was that the March 24, 2008 restriction requirement was somehow withdrawn in whole. (*See, e.g.*, April 13, 2018 Joint Invalidity Contentions at 25; D.I. 170 at ¶¶ 1369-70, 1375-76, 1378, 1385.) This argument is baseless, and Mr. Carmichael did not provide any testimony to support it at trial. (Carmichael 1317:3-10.) Instead, he testified about his unsupported and meritless "voluntary acts" opinion, which was raised for the first time during expert discovery and is discussed in more detail below.

[74] Zydus's only other argument in its Invalidity Contentions for why the Section 121 safe harbor does not apply in this case was that the "consonance" requirement for obtaining the safe harbor protection was somehow not met. (*See, e.g.*, April 13, 2018 Joint Invalidity Contentions at 25; D.I. 170 at ¶¶ 1448-1456.) Zydus, again for the first time at trial, conceded that it was no longer challenging consonance. (Plaintiffs' Opening 1189:5-16.) Nonetheless, Mr. Stoll confirmed that

193. On March 24, 2008, the Examiners issued an office action restricting pending claims 1-55 into more than 140 patentably distinct invention groups, which fell into four general categories: (1) compounds; (2) methods of treatment; (3) processes for preparing/making; and (4) compositions comprising compounds and another therapeutic agent. (Stoll 1201:19-1204:14, PDX-704; PTX-1058.0002-.0015; *see also* Carmichael 1313:6-13, 1313:22-1314:8.)

194. The Examiners' June 2, 2009 Notice of Allowance withdrew this restriction requirement only with respect to "the rejoined inventions" (*i.e.*, process-of-making claims 38 and 39). (Stoll 1224:8-1226:22, PDX-708; PTX-1064.0007.) The restriction requirement remained in place for the other 140-plus non-elected invention groups, including the method-of-treatment claims. (*Id.*) The Examiners confirmed that the June 2, 2009 Notice of Allowance withdrew the restriction requirement only as to process-of-making claims 38 and 39 in their subsequent June 21, 2010 and October 15, 2020 Notices of Allowance. (Stoll 1233:14-1236:15; PDX-711; PTX-1065.0006-.0007; PTX-1066.0005-.0006.)

195. MTPC subsequently filed the method-of-treatment claims as a divisional application, which ultimately led to the '219 patent.[75] (Stoll 1238:4-1239:7, PDX-712; PTX-0005.0004, .0030-.0306, .0379-.0382.) Absent the restriction requirement—which was still in place at the conclusion of the '788 patent prosecution—MTPC could have retained the method-of-treatment claims in the same application as the compound claims of the '788 patent, and all of the claims would have expired together on July 14, 2027. (Stoll 1217:11-1218:2,

---

consonance was properly maintained (Stoll 1195:23-1196:1, 1244:5-7), and Mr. Carmichael did not dispute that opinion (Carmichael 1325:22-1326:4).

[75] This application was a divisional of U.S. Patent Application No. 13/005,757, which itself was a divisional of the application that led to the '788 patent. (Stoll 1238:4-1239:7, PDX-712; PTX-0005.0030) Zydus did not dispute that this divisional chain satisfied the requirements of the Section 121 safe harbor. (COL ¶¶ 251-52.)

1222:25-1223:15, 1231:14-23; Plaintiffs' Opening 1183:6-25, PDX-616.) Accordingly, the '219 patent was filed as a result of the Examiners' restriction requirement, and the '788 patent claims are protected from any obviousness-type double patenting assertion based on the '219 patent by the 35 U.S.C. § 121 safe harbor. (COL ¶¶ 251-52.)

(2) Zydus's Misinformed and Legally Baseless "Voluntary Acts" Argument Does Not Defeat the 35 U.S.C. § 121 Safe Harbor

196. Despite abandoning ***every one*** of the arguments it made in its April 3, 2018 Invalidity Contentions (*see supra* ¶ 192 n.73, n.74), Zydus continued to dispute at trial the application of the safe harbor by attempting to manufacture a new legal requirement.[76] Specifically, Zydus argued that, even where a restriction requirement was in place, a proper divisional application was filed, and consonance was maintained, the safe harbor allegedly does not apply because there was no requirement that the applicant cancel the method-of-treatment claims. Therefore, according to Zydus, it was a "voluntary act." (Zydus's Opening 1167:3-9.) Zydus has not provided any case law to support this novel legal proposition because there is none. In fact, Zydus's new argument is flatly inconsistent with Federal Circuit precedent. (COL ¶¶ 253-55.) In any event, Zydus's position is not supported by the facts of this case.

a. Mr. Carmichael's Legal Opinion Is Not Supported by PTO Practice and Procedure

197. As Mr. Carmichael admitted, PTO practice and procedure directly conflicts with Zydus's legal argument. Specifically, the PTO procedure that was applied by the Examiners during prosecution, MPEP § 821.04(b), provides that the safe harbor "encompass[es]" a situation "where an applicant ***voluntarily cancels*** claims" directed to a restricted invention group while

[76] It was readily apparent from his testimony that Mr. Carmichael offered what amounted to an improper statutory and legal interpretation of the "as a result of" requirement in 35 U.S.C. § 121. (COL ¶¶ 251, 253-54.)

the restriction requirement is still in place. (Carmichael 1323:25-1325:21, PTX-1053.0069; *see also* Stoll 1233:17-1234:14, 1233:14-1236:15, 1242:8-1243:15, PDX-711, PDX-713-714; PTX-1064.0007; PTX-1065.0006-.0007; PTX-1066.0005-.0006.)

198. Although the MPEP discusses when the safe harbor would not apply under PTO procedure, it is clear that this occurs only when an applicant presents claims in a divisional application where "no restriction requirement was made by the office."[77] (Stoll 1242:8-1243:7, PDX-713; PTX-1053.0065.) This is consistent with Federal Circuit precedent, where, because an applicant voluntarily filed a divisional application after the examiner had withdrawn the restriction requirement, the applicant was not "forced [to file the divisional] ***by the restriction requirement***." *In re Ziegler*, 443 F.2d 1211, 1215-14 (C.C.P.A. 1971) (emphasis added). As explained at trial, this is not what happened here.

b. The Examiners Did Not Permit Rejoinder of the Method-of-Treatment Claims

199. Even if Zydus's "voluntarily acts" argument was legally cognizable (it is not), it is contradicted by the evidence presented at trial.

200. In response to the Examiners' March 24, 2008 restriction requirement, MTPC elected the compound Invention Group No. I. (Stoll 1209:17-1210:21; PTX-1059.0015.) MTPC requested to rejoin the non-elected method-of-treatment claims once elected compound claims—which included canagliflozin as the elected species (Stoll 1210:13-21; PTX-1059.0015)—were deemed allowable. (Stoll 1211:9-17; PTX-1059.0016; *see also* Carmichael 1329:4-5.)

201. On June 16, 2008, the Examiners allowed claims 56 and 57, which covered the compound canagliflozin. (Stoll 1212:4-1213:3; PTX-1059.0013-.0014; PTX-1060.0002-.0003.)

[77] Mr. Carmichael did not dispute Mr. Stoll's interpretation of these PTO procedures and, in fact, did not affirmatively testify about any specific MPEP provision to support his opinions.

Effectively denying MTPC's request for rejoinder, however, the Examiners withdrew, *inter alia*, non-elected method-of-treatment claims 58-61 from consideration despite that they contained all of the limitations of allowed claim 56. (Stoll 1212:4-1214:13, 1215:24-1216:8, PDX-706; PTX-1059.0013-.0014; PTX-1060.0002-.0003.)

202. In response, on September 15, 2008, MTPC requested rejoinder of the method-of-treatment claims for a ***second time***, as certain of them contained all of the limitations of the then-allowed compound claims. (Stoll 1216:9-1218:14, 1220:15-1221:9, PDX-706-07; PTX-1061.0003, .0009, .0011-.0012, .0014, .0017.) MTPC further specifically reserved the right to pursue any cancelled subject matter in separate applications (Stoll 1218:15-1219:2; PTX-1061.0014), and Mr. Carmichael did not testify about any PTO procedure that would have prevented MTPC from reserving this right.

203. Even after allowing, *inter alia*, claim 10 on December 5, 2008, the Examiners still did not permit MTPC's request to rejoin the method-of-treatment claims 32-33 and 58-61[78] despite the fact that they contained all of the limitations of (and expressly incorporated) then-allowed claims 10 and 56, respectively.[79] (Stoll 1213:17-1214:10, 1219:3-1221:13, PDX-706-07; PTX-1059.0013-.0014; PTX-1061.0003, .0009; PTX-1062.0003.)

---

[78] Recognizing his opinions are further undermined by the Examiners' rejection of MTPC's second attempt to rejoin the method-of-treatment claims, Mr. Carmichael resorted to characterizing MTPC's second request for rejoinder as "conditional," which the plain language of that request reveals is without merit. (*Compare* Carmichael 1330:12-1332:10 *with* PTX-1061.0017 ("At this point, Claims 38 and 39, directed to a process of preparation, and Claims 32, 33, and 58-61, directed to method of treatment, ***should be rejoined*** since allowable generic and linking claims are present in the application.") (emphasis added).)

[79] Mr. Carmichael testified (without any support) that an Examiner cannot consider rejoinder of non-elected claims until all pending compound claims are allowed. (Carmichael 1307:6-25.) There is nothing in the MPEP that prevents an examiner from considering rejoinder of claims at any time. (*See, e.g.*, Stoll 1247:8-13.)

204. Only after MTPC expressly notified the Examiners that it could cancel non-rejoined claims, and the Examiners refused its second request to rejoin the non-elected method-of-treatment claims, did MTPC cancel those claims on March 3, 2009, to expedite prosecution of the application. (Stoll 1218:3-1219:2, 1221:16-1222:24; PTX-1061.0014; PTX-1063.0011.) As Mr. Stoll explained, the standard PTO procedure in such a situation—where an examiner had already (twice) rejected the applicant's request to rejoin method-of-treatment claims following the issuance of a restriction requirement—would be to cancel the claims and file a divisional application because a patent cannot issue while withdrawn, non-elected claims are pending. (Stoll 1222:8-1223:15, 1231:9-1232:17, PDX-710; PTX-1053.0069.)

205. Zydus and Mr. Carmichael insisted that MTPC acted "voluntarily" by cancelling the method-of-treatment claims because there was no "administrative requirement" to cancel them. (*See, e.g.*, Zydus's Opening 1166:1-9; Carmichael 1283:3-18.) But, again, MTPC was not required by the PTO to continue attempting to rejoin the method-of-treatment claims to preserve the protection of the Section 121 safe harbor. (Stoll 1217:11-1218:2, 1222:8-13.) To create such an additional administrative requirement would result in, among other things, significant delays at the PTO because applicants would be required to continually request (and examiners to continually refuse) rejoinder throughout prosecution to retain the benefit of the safe harbor. (*See id.*; *see also id*. 1222:25-1223:15, 1248:24-1249:5.)

206. Mr. Carmichael did not testify about any PTO procedure to support this opinion because none exists. In fact, such a requirement would be inconsistent with MPEP 821.04(b). (*See supra* ¶ 197.) Specifically, as of March 3, 2009, MTPC had cancelled "all the claims directed to a non-elected process invention [*i.e.*, the method-of-treatment claims] before

rejoinder occur[ed]" on June 2, 2009.[80] (Stoll 1221:16-1222:7; PTX-1063.0011; PTX-1053.0069; Carmichael 1309:10-11, 1335:4-1336:1 (admitting that "all the method of treatment claims" had been cancelled "before rejoinder").) There is no dispute that the Examiners did not "withdraw the restriction requirement" with respect to these non-elected claims, which "[would] preserve applicant's rights under 35 U.S.C. 121." (Stoll 1231:9-1232:17, PDX-710; PTX-1053.0069; Carmichael 1317:3-10.)

c. After MTPC Cancelled the Method-of-Treatment Claims, the Examiners Never Indicated That They Could Be Rejoined

207. After MTPC cancelled the method-of-treatment claims, the Examiners sent a Notice of Allowance on June 2, 2009, in which they partially withdrew the restriction requirement to allow a limited rejoinder of the process-of-making claims. (Stoll 1224:8-1225:2, PDX-708; PTX-1064.0007.) As Mr. Stoll explained, the Examiners carefully tracked the language of MPEP form paragraph 8.43, but removed the reference to the process "of using" (*i.e.*, method-of-treatment) claims to ensure that the restriction requirement remained in place with respect to the non-elected method-of-treatment invention groups, pursuant to PTO procedure. (*Id.*; *see also* Stoll 1200:1-23, 1225:20-1226:22, PDX-708, PDX-703.)

208. Mr. Carmichael implied that, because the Examiners did not expressly mention the method-of-treatment claims in the Notice of Allowance, the applicants should have requested rejoinder of those claims. (Carmichael 1308:18-1309:21.) Mr. Carmichael's testimony is premised on his incorrect position that examiners cannot discuss or rejoin claims once they are cancelled. (*Id.* 1309:5-21.) As Mr. Stoll explained, an Examiner "***must***" notify an applicant if

[80] MTPC and the Examiners referred to method-of-treatment claims, which is a term used in the pharmaceutical context for what the MPEP calls "process of use" claims. (Stoll 1203:5-14, 1205:19-1206:6, PDX-705; PTX-1058.0015-.0016; PTX-1053.0049.)

claims can be rejoined, even if those claims were previously cancelled. (Stoll 1228:17-1230:21; PTX-1053.0067; *see also* Carmichael 1318:11-1320:13, 1321:21-1322:2 (admitting that he did not consider the relevant sections of the MPEP on this issue).) And, Mr. Carmichael admitted that the Examiner never indicated that the method-of-treatment claims could be rejoined at any point during the prosecution of the '788 patent.[81] (Carmichael 1318:11-1320:13, 1321:21-1322:2.)

d. The 35 U.S.C. § 121 Safe Harbor Applied During the '219 Patent Prosecution

209. Primary Examiner Bland—one of the examiners for the application that led to the '788 patent—also examined the '219 divisional application. (Stoll 1238:15-1239:7, PDX-712; PTX-1058.0022; PTX-0005.0379-.0382.) Primary Examiner Bland did not indicate any issue with the divisional status of the '814 application (Stoll 1239:8-13; PTX-0005.0379-.0382) and did not reject any of the claims of the pending '219 patent over the issued claims of the '788 patent for obviousness-type double patenting consistent with the safe harbor.[82] (Stoll 1239:14-22; PTX-0005.0379-.0382.)

210. But for the Examiners' restriction requirement during the prosecution of the '788 patent, the claims of the '219 patent would have issued in the earlier patent application and thus had a longer term. (Stoll 1217:11-1218:2, 1222:25-1223:15, 1231:14-23; Plaintiffs'

[81] Mr. Carmichael also pointed to the two Requests for Continued Examination MTPC filed after the first notice of allowance. (Carmichael 1297:2-17, 1299:4-16.) Although MTPC had the right to continue to request rejoinder of the method-of-treatment claims for a third time in those requests, there is no PTO procedure requiring such an action to preserve the safe harbor protection provided by Congress. (Stoll 1217:11-16, 1222:8-13.) As discussed in paragraphs 205-06 above, such a requirement would be both inconsistent with MPEP § 821.04(b) and cause significant delays at the PTO.

[82] Examiners are presumed to have followed PTO requirements and executed their duties properly. (COL ¶ 241.) Zydus has not provided any evidence that Examiner Bland made a mistake during prosecution.

Opening 1183:6-25, PDX-616.) Zydus did not prove at trial that the full term of the '788 patent should be shortened. Instead, MTPC's compliance with the Examiners' restriction requirement is the exact situation that the safe harbor provision of 35 U.S.C. § 121 was designed to protect. (COL Section VII.D.2.)

VII. CONCLUSIONS OF LAW

A. This Court Has Jurisdiction

211. This a patent-infringement action brought under 35 U.S.C. § 271 and the Hatch-Waxman Act, 21 U.S.C. § 355(j). (SF ¶¶ 12, 14.) This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). (SF ¶ 13) Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b). (*Id.*)

B. Zydus's ANDA Products Infringe the Asserted Claims

212. Zydus has stipulated that its submission of ANDA Nos. 210541 and 210542 to the FDA and the commercial manufacture, use, offer for sale, sale, or importation of Zydus's ANDA Products before the expiration of the asserted claims constitutes literal infringement pursuant to 35 U.S.C. § 271. (SF ¶ 17; D.I. 100.)

C. Zydus Did Not Prove by Clear and Convincing Evidence That the Asserted Claims Would Have Been Obvious under 35 U.S.C. § 103

213. Zydus did not prove by clear and convincing evidence that the prior art would have motivated a POSA to select the '117 patent compound as a "lead compound" and then make four simultaneous, significant structural changes to the '117 patent compound over numerous other potential changes. Zydus also did not prove by clear and convincing evidence that a POSA would have had a reasonable expectation that those four significant structural changes would result in an improved antidiabetic compound for treating type 2 diabetes.

(1) Applicable Legal Standards for Zydus's Obviousness Arguments

214. Under 35 U.S.C. § 282, the asserted claims are presumed valid. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011). Zydus therefore bears the burden of proving obviousness under 35 U.S.C. § 103 by "clear and convincing evidence."[83] *Id.*

215. Under 35 U.S.C. § 103, a patent claim is valid unless the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to a POSA. *See* 35 U.S.C. § 103. In conducting an obviousness analysis, the following factors must be considered:

- the scope and content of the prior art;
- the differences between the prior art and the claimed invention;
- the level of ordinary skill in the relevant art; and
- any objective indicia of nonobviousness, including unexpected properties, skepticism, failure of others, copying and acquiescence, and commercial success.

See, e.g., *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1290 (Fed. Cir. 2012) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

216. The obviousness inquiry entails considering whether a POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and would have had a reasonable expectation of success in doing so." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859-61 (Fed. Cir. 2015). An important aspect of the "motivation" analysis is identifying the "problem facing those skilled in the art at the time the invention was made," which "is not [limited to] the specific problem solved by the invention." *Id.* at 859-60

[83] Although the standard remains "clear and convincing evidence," Zydus "bears a difficult burden" here because it relies on prior art that was before the PTO examiners. *Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1375 (Fed. Cir. 2015); *see also* PFOF ¶ 35 n.8.

("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.").

217. Where a patent claim covers a previously unknown chemical compound, the patent challenger must *first* identify, by clear and convincing evidence, a discrete number of "lead compounds, or starting points" from the prior art that would have been selected "for further development" by the POSA. *Otsuka*, 678 F.3d at 1291. *Second*, the patent challenger must then establish, by clear and convincing evidence, that the prior art would have motivated the POSA to modify that particular lead compound to arrive at the claimed compound with a reasonable expectation that the new compound would have the desired properties. *See, e.g., id.* at 1292.

(2) The POSA and the Problem to Be Solved with Respect to the Patents-in-Suit

218. There is not dispute that a POSA in this case would have had a graduate degree in medicinal chemistry, pharmacology, and/or related field, with experience in the development of pharmaceutical compositions and an awareness of the antidiabetic drug field. (PFOF ¶ 36.)

219. The undisputed evidence in this case shows that the date of invention of the subject matter of the asserted claims was no later than October 29, 2003. (PFOF ¶ 37.)

220. The undisputed evidence in this case shows that the problem faced by a POSA would have been to develop an improved antidiabetic drug. (PFOF ¶¶ 38-39.)

(3) Zydus Did Not Prove That a POSA Would Have Selected the '117 Patent Compound as a Lead Compound

221. A lead compound is a "compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). "[T]he analysis is guided by evidence of the compound's pertinent properties." *Otsuka*, 678 F.3d at 1292. "[P]roving a reason to select a compound as a lead compound depends on more than

just structural similarity, but also ***knowledge in the art*** of the functional properties and limitations of the prior art compounds." *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (emphasis added).

222. Zydus did not prove, by clear and convincing evidence and without the use of hindsight, that a POSA would have selected the '117 patent compound as a lead over other, more favorable antidiabetic treatment options, especially given the lack of any known biological data for that compound in the prior art. *See, e.g.*, *Daiichi*, 619 F.3d at 1353-54 (rejecting proposed lead compounds because a POSA would not have selected them over a handful of "more thoroughly studied" compounds having more advanced data); *see also Merck Sharp & Dohme Corp. v. Sandoz Inc.*, No. 12-3289, 2015 WL 5089543, at *43 (D.N.J. Aug. 27, 2015) ("As in *Daiichi*, the lack of pharmaceutical data available on the [proposed lead] compound in question renders [the claimed invention] non-obvious in light of the available data on other compounds."); *see also* PFOF Section III.B.[84]

(4) Zydus Did Not Prove That a POSA Would Have Been Motivated to Make the Specific Molecular Modifications to the '117 Patent Compound Needed to Arrive at the Claimed Invention

a. A POSA Would Not Have Been Motivated to "Design Around" the BMS Patents in Pursuit of a "Me Too" Compound

223. Zydus did not prove that a POSA faced with the problem of developing an improved antidiabetic drug would have been motivated to "design around" the BMS patents

[84] Zydus relies on *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014), to support its hindsight-based lead compound selection. (D.I. 165 at 10-11.) The lead compound in that case, however: (1) had publicly available biological data, including "better *in vitro* antiviral activity . . . than the FDA-approved best-selling drug at the time"; and (2) researchers "were actually treating and using" that compound as a lead ***in the prior art***. *Bristol-Myers Squibb*, 752 F.3d at 971, 974. Zydus did not present any such prior art evidence at trial to support its lead compound selection here. (PFOF ¶¶ 54-57.)

simply to maintain "comparable," "me too" activity. *See, e.g.*, *InSite*, 783 F.3d at 859-61 (affirming rejection of defendant's "overly narrow" problem faced by the POSA to avoid improper hindsight); *Otsuka*, 678 F.3d at 1291 (defining a lead compound as a "compound in the prior art that would be most promising to modify in order to ***improve upon*** its . . . activity and obtain a compound with better activity") (emphasis added); *see also* PFOF ¶¶ 38-39.

224. Similarly, Zydus did not prove that a POSA faced with the problem of developing an improved antidiabetic drug would have been motivated to pursue modifications to the '117 patent compound that provided "roughly equal[]" properties. *See, e.g.*, *InSite*, 783 F.3d at 859-61; *Otsuka*, 678 F.3d at 1291; *see also* PFOF ¶¶ 77-78. This is particularly true given that such a motivation would apply equally to numerous other options in the prior art. (*See* PFOF Section III.D; COL ¶ 231.)

b. A POSA Would Not Have Been Motivated to Change the Distinguishing Features of the '117 Patent Compound

225. Zydus's assertion that a POSA would have replaced both the 4-chloro and 4-ethoxy groups of the '117 patent compound is inconsistent with Federal Circuit law because it would have required the POSA to disregard the only two features that would have allegedly justified selecting that compound as a lead in the first place. *See, e.g., Daiichi,* 619 F.3d at 1356 (affirming that a POSA does not select a lead compound "only to disregard one of their distinguishing characteristics"); *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1358-59 (Fed. Cir. 2008) ("The record, however, shows no discernible reason for a skilled artisan to begin with [a lead compound] only to drop the very feature . . . that gave this advantageous property."); *see also* PFOF ¶ 74.

c. Each of Zydus's Four Alleged Changes Suffers from Additional Problems Based on the Prior Art

226. *First*, Zydus failed to prove by clear and convincing evidence that a POSA would have understood the 4-chloro and 4-methyl groups to be "roughly equal[]" options because the prior art disclosed—consistent with Zydus's own assertions in another case (PFOF ¶ 80)—that such a methyl group could create metabolic instability, a problem that Zydus acknowledges a POSA would have wanted to avoid. *See, e.g.*, *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000) (explaining that "[a] reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant"); *see also* PFOF Section III.C.1.

227. *Second*, Zydus did not prove by clear and convincing evidence that a POSA would have been motivated to change the phenyl B Ring to a thiophene ring based upon general "bioisosterism" principles because such an assertion falls far short of demonstrating the requisite motivation to make a specific molecular modification. *See, e.g.*, *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 689 F.3d 1368, 1374-75, 1377-78 (Fed. Cir. 2012) (finding "bioisosterism" would not have motivated ***thiophene-to-phenyl*** change); *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344-45 (Fed. Cir. 2000) (rejecting "bioisosteric substitution" theory); *Mylan Pharm. Inc. v. Research Corp. Techs., Inc.*, 914 F.3d 1366, 1376 (Fed. Cir. 2019) (same); *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 543 (D. Del. 2016) ("[A] POSA would not have been able to predict the effect of a bioisosteric substitution," which "can change the way a molecule interacts with biological receptors" and "drastically impact drug performance"), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018); *see also* PFOF

Section III.C.2.b.[85] In any event, the evidence at trial showed that a POSA would have understood the phenyl ring structure to be critical to the activity of the C-glucosides on which Zydus focuses, which would have taught away from this change. *See, e.g.*, *Daiichi*, 619 F.3d at 1354-55 (affirming teaching away from a specific substitution where "the vast majority, thirty-six out of forty-two compounds," did not possess that substitution); *Winner*, 202 F.3d at 1349-50 (explaining that teaching away "alone can defeat [an] obviousness claim"); *see also* PFOF Section III.C.2.a, III.C.2.c.

228. *Third*, Zydus did not prove by clear and convincing evidence that a POSA would have been motivated to continue making a third change, let alone substitute a new phenyl ring for the 4-ethoxy group "to solve an undefined problem" that was allegedly created by Zydus's proposed thiophene change.[86] *See, e.g.*, *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087 (Fed. Cir. 2019); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1353, 1356-57

---

[85] Zydus relied on *In re Merck Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986), and *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330 (D. Del. 1991), to support its various "bioisosterism" arguments. (*See* D.I. 165 at 13, 16.) *In re Merck*, however, did not rely on bioisosterism as motivation to modify a prior art compound because it concerned a ***method of using an already known compound***. *In re Merck*, 800 F.2d at 1092, 1094, 1097 (relying on bioisosterism only "[i]n combination with" prior art clearly suggesting claimed invention as additional support for reasonable expectation of success requirement); *see also* Plaintiffs' Opening 69:9-71:21. Similarly inapposite, the non-binding *Imperial* decision found only that "the ***expectation*** that almost any 'R' group would result in a beta-blocker," where the compound set forth in the method-of-treatment claim at issue merely "turned around" the "R" group in a prior art compound known to work for the same method of treatment, was "***also enhanced*** [by] guidelines developed for 'bioisosteri[c]' replacements." 777 F. Supp. 330, 347-48, 351 (D. Del. 1991) (emphasis added). Here, Zydus has alleged that a POSA would have made multiple simultaneous modifications, not all of which are even alleged to be bioisosteric, without any SGLT prior art data supporting its proposed changes.

[86] Zydus claimed before trial that this was another "bioisosteric" change. (D.I. 170 at ¶¶ 723-27, 730.) At trial, however, Zydus's own expert did not support this position—because it, like Zydus's obviousness defense as a whole, is "utterly frivolous." *See, e.g.*, *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 549 F.3d 1381, 1389 (Fed. Cir. 2008) (affirming exceptional case based upon "bioisostere" argument); *see also* PFOF ¶ 100.

(Fed. Cir. 2013) (finding that a modification would not have been obvious because the POSA "would not have recognized the problem" even existed); *see also* PFOF Section III.C.3.

229. *Fourth*, Zydus did not prove by clear and convincing evidence that a POSA would have continued changing any new distal phenyl ring by adding a 4-fluoro to allegedly solve another problem created by Zydus's own proposed changes. *See, e.g.*, *Amerigen*, 913 F.3d at 1087; *Leo*, 726 F.3d at 1353, 1356-57; *see also* PFOF Section III.C.4.

d. A POSA Would Not Have Been Motivated to Make All Four Proposed Changes at the Same Time While Ignoring All Other Options

230. Zydus did not prove, by clear and convincing evidence and without the benefit of hindsight, that a POSA would have been motivated to make all four of its alleged changes, one after another, without testing the effects of any one of them. (PFOF Section III.C.) A POSA would not act in such an irrational manner. *See, e.g.*, *Yamanouchi Pharm. Co. v. Danbury Pharmacal*, 21 F. Supp. 2d 366, 373 n.13 (S.D.N.Y. 1998) (explaining that a POSA "thinks along the line of conventional wisdom" and does not "innovate," including through "expensive, systematic research or by extraordinary insights"), *aff'd*, 231 F.3d 1339 (Fed. Cir. 2000).

231. Moreover, Zydus did not prove by clear and convincing evidence that a POSA would have made these four specific changes and ignored the countless other options she would have faced according to Zydus's motivation analysis. *See Takeda*, 492 F.3d at 1356 (finding a failure to provide the requisite motivation to make "specific molecular modifications necessary to achieve the claimed invention" because of numerous other potential prior art modifications); *see also Eli Lilly*, 689 F.3d 1378 ("[A] complicated compound such as the '608 Compound provides many opportunities for modification, but the district court did not find that substituting a phenyl group into the aryl position ***was the one, among all the possibilities***, that would have been successfully pursued.") (emphasis added); *Sanofi-Aventis U.S. LLC v. Dr. Reddy's Labs.*,

933 F.3d 1367, 1380 (Fed. Cir. 2019) (finding no motivation to make multiple simultaneous modifications where "numerous [other] modifications were under investigation" in the prior art); *see also* PFOF Section III.D.[87]

e. Zydus Cannot Prove That Its Alleged Changes Would Have Been "Obvious to Try"

232. Zydus did not prove by clear and convincing evidence that the prior art options were "finite," "small," or "easily traversed," especially considering the difficulties of satisfying the "obvious to try" standard in chemical compound cases. *In re Cyclobenzaprine*, 676 F.3d 1063, 1072-73 (Fed. Cir. 2012) ("[W]here the prior art, at best, gives only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible."); *see also Takeda*, 492 F.3d at 1359 (rejecting "obvious to try" rationale in chemical compound case).

233. There would have been countless options that a POSA would have needed to consider, without any specific guidance, under Zydus's impermissible "obvious to try" analysis. (PFOF Section III.E.)

(5) Zydus Did Not Prove That a POSA Would Have Had a Reasonable Expectation of Success

234. In light of the numerous examples of unpredictability in the SGLT field and Zydus's lack of prior art support,[88] Zydus did not prove by clear and convincing evidence that a

[87] Zydus reliance on *Bristol-Myers Squibb* (*see, e.g.*, D.I. 165 at 9, 12-13) in support of its four proposed changes is also misplaced, as the lead compound in that case required a single "small" and "conservative" change. 752 F.3d at 972, 974-75. As the Federal Circuit recently explained, "*Bristol-Myers Squibb* [involved] a single chemical change to a lead compound where there were a 'small, finite number of changes to try,' and the particular claimed change had already been shown to have desirable properties in a similar context" in the prior art. *Sanofi*, 933 F.3d at 1380 (determining that prior art did not support that proposed changes would "***improve[]*** activity") (emphasis added).

POSA would have reasonably expected its numerous and significant proposed modifications to result in an SGLT compound that was selective, efficacious after oral administration, and non-toxic. *See, e.g.*, *Yamanouchi*, 231 F.3d at 1345 (defining "success" as "finding a compound that had high activity, few side effects, and lacked toxicity"); *Takeda*, 492 F.3d at 1360 (affirming no reasonable expectation of success where prior art provided no data showing that "adding a methyl group . . . would reduce or eliminate its toxicity"); *Merck*, 2015 WL 5089543, at *29 (finding no reasonable expectation of success "[w]ithout the benefit of any biological and pharmacokinetic data"); *see also* PFOF Section III.F.

* * *

235. Through numerous rulings, the Federal Circuit has made clear that even supposedly "minor" modifications of a chemical compound can be nonobvious, and ***not a single case has found*** that four significant changes to a lead compound would have been obvious. *See, e.g.*, *Eli Lilly*, 689 F.3d 1368;[89] *Otsuka*, 678 F.3d 1280; *Takeda*, 492 F.3d 1350; *Eisai*, 533 F.3d 1353; *see also* PDX-50 (discussed at Plaintiffs' Opening 82:11-83:21).

(6) Zydus Did Not Prove by Clear and Convincing Evidence That Claim 22 of the '219 Patent and Claim 26 of the '403 Patent Would Have Been Obvious

236. Even if Zydus proved obviousness with respect to claims 12 and 20 of the '788 patent (which it did not), Zydus failed to offer any evidence—let alone clear and convincing evidence—at trial that the additional limitations of claim 22 of the '219 patent and claim 26 of

---

[88] "[T]o the extent an art is unpredictable, as the chemical arts often are . . . potential solutions are less likely to be genuinely predictable." *Eisai*, 533 F.3d at 1359.

[89] The Federal Circuit's *Eli Lilly* decision alone justifies rejecting Zydus's obviousness defense. In that case, a proposed thiophene-to-phenyl "bioisosteri[c]" change lacked supporting data in the relevant prior art, which would have "dissuaded" a POSA from making this substitution. 689 F.3d 1377-78. The same is true here.

the '403 patent would have been obvious to a POSA. (PFOF Section IV.) As such, Zydus cannot meet its burden to prove obviousness of these claims by clear and convincing evidence. *See, e.g.*, *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc*., 694 F.3d 1312, 1327-28 (Fed. Cir. 2012) (finding that conclusory expert opinions do not suffice to prove obviousness).

(7) Objective Indicia of Nonobviousness Confirm That Zydus Did Not Prove Obviousness of the Asserted Claims by Clear and Convincing Evidence

237. Because Zydus failed to prove, by clear and convincing evidence and without hindsight, the lead compound, motivation to modify, and reasonable expectation of success requirements for obviousness, consideration of objective indicia of nonobviousness is unnecessary. *See, e.g.*, *Yamanouchi*, 231 F.3d at 1345 ("Because [defendant] did not show even a *prima facie* case for obviousness, this court has considered, but need not separately address, the strong objective evidence of non-obviousness."); *Takeda*, 492 F.3d at 1363 (same). Further, despite Zydus's claims, even the absence of objective indicia is a "neutral factor" that does not weight in favor of obviousness "because such evidence is not a requirement for patentability." *See, e.g.*, *Custom Accessories, Inc. v. Jeffrey-Allan Indus*., 807 F.2d 955, 960 (Fed. Cir. 1986).

238. Nonetheless, Zydus carries the burden of establishing obviousness of the asserted claims by clear and convincing evidence, and that burden remains with Zydus even when relevant objective indicia are considered. *See, e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1078 n.5, 1079 (explaining there is no "burden-shifting framework" in the context of obviousness). The evidence of objective indicia presented at trial only further confirms that Zydus's obviousness allegations are infected with hindsight and disconnected from real-world facts. *See, e.g.*, *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013).

239. Because the Invokana® Products are the commercial embodiments of the asserted claims, and their properties flow from the active ingredient canagliflozin, a nexus is presumed.

See, e.g., *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); *see also* PFOF ¶ 143. Zydus did not present any evidence at trial rebutting this presumed nexus.

240. **Unexpected properties:** Canagliflozin has demonstrated unexpected superior clinical outcomes when compared to the '117 patent compound, as demonstrated by clinical data and their FDA-approved labels, which "yielded more than predictable results." *See, e.g.*, *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) ("Unexpected results are shown in comparison to what was known, not what was unknown"); *see also* PFOF Section V.A. Zydus's attempt to refute such evidence by applying an FDA standard "confuses the requirements under the law for obtaining a patent with the requirements for obtaining [FDA] approval," *see, e.g.*, *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995), where the patent laws have long recognized that an "indirect showing of unexpected superiority will rebut" obviousness, *see, e.g.*, *In re Fenn*, 639 F.2d 762, 765 (C.C.P.A. 1981).[90]

241. **Skepticism:** Skepticism surrounded the development of SGLT inhibitors as a potential diabetes treatments in the 2003 time period, which resulted in many top pharmaceutical companies directing resources to other approaches. *See, e.g.*, *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1367 (Fed. Cir. 2012) (noting that the industry's skepticism supported nonobviousness where the plaintiff "offered evidence that leading experts in the field were skeptical"); *WBIP*, 829 F.3d at 1335 ("If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness."); *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019) (recognizing "a range of third-party opinion that can constitute

[90] The decisions of the former Court of Customs and Patent Appeals are "binding as precedent" on the Federal Circuit. *E.g.*, *S. Corp. v. United States*, 690 F.2d 1368, 1369 (Fed. Cir. 1982).

skepticism," including statements about third parties being "worried" or "surprised"); *see also* PFOF Section V.B.

242. **Failure of others:** Zydus does not dispute that there was a long-felt need for an improved antidiabetic and that a number of pharmaceutical companies tried, but failed, to develop an SGLT inhibitor drug product to meet this need. *See, e.g., In re Cyclobenzaprine*, 676 F.3d at 1082 ("Longfelt need is closely related to the failure of others. Evidence is particularly probative of [non]obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand."); *see also* PFOF Section V.C.

243. **Copying and Acquiescence:** At least 14 generic pharmaceutical companies are seeking to market generic Invokana® Products, but Zydus is the only one alleging that the asserted claims would have been obvious. *Cf.*, *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004) (finding that eight companies respecting the patents-in-suit by seeking a license constituted objective evidence of nonobviousness); *see also* PFOF Section V.D.

244. **Commercial success:** The Invokana® Products have been commercially successful by any measure, which would have motivated competitors to develop them earlier if canagliflozin was, in fact, obvious. *See, e.g., Eisai,* 533 F.3d at 1356 ("Aciphex has been a commercial success, garnering over $1 billion in worldwide yearly sales."); *see also* PFOF at Section V.E.

D. Zydus Did Not Prove Obviousness-Type Double Patenting by Clear and Convincing Evidence

(1) A Judge-Made Doctrine Should Not Be Used to Negate the '788 Patent's Statutorily Authorized PTA

245. Zydus did not prove that the '219 patent can serve as a proper basis for invalidating the '788 patent's PTA under the judicially created obviousness-type double

patenting doctrine. Congress statutorily prescribed such a term adjustment as a "Patent Term Guarantee[]," where "the term of the patent ***shall be extended***" to compensate the patent applicant for PTO delays that occur during patent prosecution. 35 U.S.C. § 154 (emphasis added); *see also* PDX-603 (discussed at Plaintiffs' Opening 1169:10-1170:6).

246. In *Novartis AG v. Ezra Ventures LLC*, the Federal Circuit held that a statutory term extension analogous to a PTA, *i.e.*, a PTE,[91] is immune from obviousness-type double patenting challenges. 909 F.3d 1367, 1375 (Fed. Cir. 2018). In doing so, the court found that the "judge-made [double patenting] doctrine" should not be used to "cut off a statutorily-authorized time extension." *Id.*; *see also* PDX-607 (discussed at Plaintiffs' Opening 1174:24-1175:17). This ruling is entirely consistent with longstanding Supreme Court precedent barring judicially created doctrines from negating a statutorily authorized right, which would give courts "a 'legislation-overriding' role that is beyond the Judiciary's power." *See, e.g.*, *SCA Hygiene Prods. Aktiebolag v. First Quality Baby Prods., LLC*, 137 S. Ct. 954, 960 (2017); *see also* D.I. 166 at 35 n.37.[92]

247. The '788 patent's PTA is likewise immune from such challenges, particularly given that, in 35 U.S.C. § 282(c), Congress equated PTAs and PTEs for purposes of defining

[91] Like a PTA, a PTE under 35 U.S.C. § 156 compensates a patentee for governmental delay. *See* 35 U.S.C. § 156(c).

[92] Zydus is incorrect that *Novartis* distinguished PTEs and PTAs in the context of obviousness-type double patenting through its discussion of "terminal disclaimers." (D.I. 165 at 28 n.17.) The *Novartis* court was merely discussing an earlier decision that noted the different statutory conditions for granting these extensions, and that a PTA cannot extend the statutory term of a patent if a terminal disclaimer had previously been filed. *Novartis*, 909 F.3d at 1371 (citing *Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1323 (Fed. Cir. 2007)); *see also* PDX-608 (discussed at Plaintiffs' Opening 1175:18-1177:21). A PTE, on the other hand, does not extend the statutory term of the patent, but rather only those claims covering, *inter alia*, a drug product under regulatory review. *See, e.g.*, *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1349 (Fed. Cir. 2010). The portion of *Novartis* focused on by Zydus does not bear on the issue presented here.

how an "extension of a patent term or any portion thereof under section 154(b) or 156" can potentially be invalidated, which does not include obviousness-type double patenting. *See* 35 U.S.C. § 282(c).

248. Zydus is incorrect that the '219 patent is "a later-issued[,] but earlier-expiring patent" that can invalidate the '788 patent based on *Gilead Scis, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014). *Gilead*, whose holding was limited to "the circumstances of [that] case," 753 F.3d at 1212, did not involve an assertion of invalidity based on a PTA; as the Federal Circuit explained in *Novartis*, "[t]he effect of statutory term extensions was expressly not considered in *Gilead*," 909 F.3d at 1375 n.2; *see also* PDX-606 (discussed at Plaintiffs' Opening 1172:15-1174:23). Instead, *Gilead* focused on preventing a "potential gamesmanship issue through structuring of priority claims." *Novartis*, 909 F.3d at 1374-75. Zydus has never asserted, and did not offer any evidence at trial demonstrating, that MTPC engaged in any such "tactics," because MTPC did not.

249. Moreover, this case does not raise the "traditional concern" with obviousness-type double patenting of extending a patent right "through claims in a later-filed patent." *Novartis*, 909 F.3d at 1374; *see also* PDX-609 (discussed at Plaintiffs' Opening 1177:22-1178:18). Instead, the first-filed '788 patent was extended beyond the expiration date of the later-filed '219 patent because of a statutorily authorized term extension based on government delay. (PFOF Section VI.A.)

(2) The '788 Patent Claims Are Protected under the 35 U.S.C. § 121 Safe Harbor

250. Irrespective of the above, the '219 patent claims are precluded from invalidating claims 12 and 20 of the '788 patent under the 35 U.S.C. § 121 safe harbor, which provides an independent basis for rejecting Zydus's defense.

251. Under 35 U.S.C. § 121, "[a] patent issuing . . . on an application filed as a result of [a restriction] requirement, shall not be used as a reference . . . in the courts against . . . the original application." As the Federal Circuit has explained, "when the existence of multiple patents is due to the administrative requirements imposed by the [PTO]" (*i.e.*, when a restriction requirement was imposed by the PTO), "35 U.S.C. § 121 provides that the inventor shall not be prejudiced by having complied with those requirements." *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568 (Fed. Cir. 1996). "The purpose of § 121 is to accommodate administrative convenience and to protect the patentee from technical flaws based on this unappealable examination practice." *Id.*; *see also Boehringer*, 592 F.3d at 1353 n.3 (noting that, "absent the restriction requirement" imposed by the PTO, "the applicant could have retained" all of the claims in the original application); *see also* PDX-612 (discussed at Plaintiffs' Opening 1178:23-180:23).

252. Under the plain language of the statute and Federal Circuit law, the safe harbor protects the '788 patent here because: (1) a restriction requirement was imposed by the Examiners, which required the separation of, *inter alia*, the compound and method-of-treatment claims; (2) this restriction requirement remained in place, including with respect to the method-of-treatment claims; and (3) the divisional '219 patent claims cover the restricted subject matter.[93] *See, e.g.*, *Boehringer*, 592 F.3d at 1353; *Applied Materials*, 98 F.3d at 1568; *see also* PFOF Section VI.B.1.

253. Zydus does not dispute that any of these elements of § 121 are met. Instead, it attempts to manufacture a new legal requirement, found nowhere in its April 13, 2018 Invalidity Contentions, that other allegedly "voluntary acts" or the applicant's "choice[s]" can somehow

[93] Zydus did not dispute that the consonance requirement of § 121 was met. (PFOF ¶ 192 n.73.)

prevent the safe harbor from applying even in the presence of a restriction requirement. (D.I. 165 at 29; Zydus's Opening 1164:16-24.) Putting aside Zydus's abandonment of every argument in its contentions on this issue, Zydus has provided no legal support for its novel statutory interpretation, which is inconsistent with Federal Circuit law.[94] In fact, in the presence of a restriction requirement, ***not a single Federal Circuit case*** has examined whether an application was filed "voluntar[il]y," or by "choice," when evaluating the applicability of the safe harbor. *See, e.g.*, *Boehringer*, 592 F.3d at 1353; *Applied Materials*, 98 F.3d at 1568; *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991); *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1179 (Fed. Cir. 1993).[95]

254. Instead, *Boehringer* confirmed that, once a restriction requirement is issued by the examiner, "the ***choice*** of how to prosecute non-elected inventions is up to the applicant and is ***constrained neither by the terms of an examiner's restriction requirement nor by the language of § 121***." *Boehringer*, 592 F.3d at 1353 & n.3 ("The child application was due to the administrative requirements imposed by the [PTO] in the sense that, ***absent the restriction requirement***, the applicant could have retained in the [original application] the claims prosecuted in the child application.") (emphases added) (internal citations and quotations omitted); PDX-618 (discussed at Plaintiffs' Opening 1184:19-1187:4).

---

[94] Zydus refers to the requirements of 35 U.S.C. § 121 as a "strict test" (D.I. 165 at 29), but overlooks that its cited support originates from *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, which explained: "Specifically, § 121 only applies to ***a restriction requirement*** that is ***documented by the PTO in enough clarity and detail to show consonance***." 349 F.3d 1373, 1382 (Fed. Cir. 2003) (emphases added). There is no dispute that this "strict requirement" is met here. (PFOF ¶ 192.)

[95] In these cases, application claims subject to a restriction requirement were eventually cancelled and pursued in subsequent applications. *See id.*

255. As such, MTPC's "choice" to file a divisional application as a result of the Examiners' restriction requirement falls squarely under the Federal Circuit's 35 U.S.C § 121 safe harbor precedent. *See Boehringer*, 592 F.3d at 1353; *Applied Materials*, 98 F.3d at 1568.

VIII. Remedies

256. Zydus failed to prove, by clear and convincing evidence and without the benefit of hindsight, that the asserted claims would have been obvious over the prior art under 35 U.S.C. § 103.

257. Zydus failed to prove, by clear and convincing evidence, that claims 12 and 20 of the '788 patent are invalid for obviousness-type double patenting over any '219 patent claim.

258. As such, Plaintiffs are entitled to an Order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of Zydus's ANDA No. 210541 be a date that is not earlier than the expiration of the '788 and '219 patents, including any patent term extension, patent term adjustment, or period of regulatory exclusivity for those patents to which Plaintiffs are or become entitled.

259. Plaintiffs are entitled to an immediate and permanent injunction restraining and enjoining Zydus from engaging in the commercial manufacture, use, offer for sale, or sale of the proposed generic products identified in Zydus's ANDA No 210541 within the United States, or importation of those products into the United States, during the term of the '788 and '219 patents and any applicable exclusivity to which Plaintiffs are or become entitled.

260. Plaintiffs are also entitled to an Order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of Zydus's ANDA No. 210542 be a date that is not earlier than the expiration of the '788, '219, and '403 patents, including any patent term extension, patent term adjustment, or period of regulatory exclusivity for those patents to which Plaintiffs are or become entitled.

261. Plaintiffs are also entitled to an immediate and permanent injunction restraining and enjoining Zydus from engaging in the commercial manufacture, use, offer for sale, or sale of the proposed generic products identified in Zydus's ANDA No 210542 within the United States, or importation of those products into the United States, during the term of the '788, '219, and '403 patents and any applicable exclusivity to which Plaintiffs are or become entitled.

Dated: November 23, 2020

Respectfully submitted,

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza, Suite 1520
Newark, NJ 07102-5426
(973) 286-6700
clizza@saul.com
wbaton@saul.com

Attorneys for Plaintiffs
Mitsubishi Tanabe Pharma Corp.,
Janssen Pharmaceuticals, Inc.,
Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International

Of Counsel:

Eric W. Dittmann
Isaac S. Ashkenazi
Dana Weir
Max H. Yusem
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166

Attorneys for Plaintiff
Mitsubishi Tanabe Pharma Corp.

Raymond N. Nimrod
Colleen Tracy-James
Catherine T. Mattes
QUINN EMANUEL
URQUHART & SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010

Attorneys for Plaintiffs
Janssen Pharmaceuticals, Inc.,
Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International